

B17

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
10 March 2005 (10.03.2005)

PCT

(10) International Publication Number
WO 2005/021515 A2

- (51) International Patent Classification⁷: C07D 261/04 (74) Common Representative: RANBAXY LABORATORIES LIMITED; c/o HEIBEL, George, E., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).
- (21) International Application Number: PCT/IB2004/002804
- (22) International Filing Date: 30 August 2004 (30.08.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/498,947 29 August 2003 (29.08.2003) US
- (71) Applicant (for all designated States except US): RANBAXY LABORATORIES LIMITED [IN/IN]; 19, Nehru Place, New Delhi, Delhi 110 019 (IN).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): PALLE, Venkata, P. [IN/IN]; D-011, Oakwood Estate, Akashneem Marg, DLF-Phase II, Gurgaon, Haryana 122001 (IN). BALACHANDRAN, Sarala [IN/IN]; A-6, National Institute of Immunology, Aruna Asif Ali Marg, New Delhi, Delhi 110067 (IN). SALMAN, Mohammad [IN/IN]; P-2/19, DLF City Phase II, Gurgaon, Haryana 122001 (IN). KUKREJA, Gagan [IN/IN]; LD-166, Sardar Patel Apartments, Pitam Pura, New Delhi 110088 (IN). GUPTA, Nidhi [IN/IN]; J-160, Vikas Puri, New Delhi (IN). RAY, Abhijit [IN/IN]; Sector C-1, 1408, Vasant Kunj, New Delhi 110070 (IN). DASTIDAR, Sunanda, G. [IN/IN]; B-138, Sarita Vihar, New Delhi 110044 (IN).
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF PHOSPHODIESTERASE TYPE-IV

(57) Abstract: The present invention relates to isoxazoline derivatives, which can be used as selective inhibitors of phosphodiesterase (PDE) type IV. In particular, compounds disclosed herein can be useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases in a patient, particularly in humans. The present invention also relates to processes for the preparation of disclosed compounds, as well as pharmaceutical compositions thereof, and their use as phosphodiesterase (PDE) type IV inhibitors.

WO 2005/021515 A2

WO 2005/021515

PCT/IB2004/002804

INHIBITORS OF PHOPHODIESTERASE TYPE-IV

Field of Invention

5 The present invention relates to isoxazoline derivatives, which can be used as selective inhibitors of phosphodiesterase (PDE) type IV. In particular, compounds disclosed herein can be useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic
10 conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases in a patient, particularly in humans. The present invention also relates to processes for the preparation of disclosed compounds, as well as pharmaceutical compositions thereof, and their use as phosphodiesterase (PDE) type IV inhibitors.

Background of Invention

15 It is known that cyclic adenosine-3',5'-monophosphate (cAMP) exhibits an important role of acting as an intracellular secondary messenger. The intracellular hydrolysis of cAMP to adenosine 5'-monophosphate (AMP) causes a number of inflammatory conditions, which include, but are not limited to, psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic
20 conjunctivitis, osteoarthritis, and ulcerative colitis. Cyclic nucleotide phosphodiesterases (PDE), a biochemically and functionally, highly variable superfamily of the enzyme, is the most important factor in the control of cAMP (as well as of cGMP) levels. Eight distinct families with more than 15 gene products are currently recognized. Although PDE I, PDE II, PDE III, PDE IV, and PDE VII all use cAMP as a substrate, only the PDE IV and PDE VII
25 types are highly selective for hydrolysis of cAMP. Accordingly, inhibitors of PDE, particularly the PDE IV inhibitors, such as rolipram or Ro-1724, are known as cAMP-enhancers. Immune cells contain PDE IV and PDE III, of which PDE IV is prevalent in human mononuclear cells. Thus, the inhibition of phosphodiesterase type IV has been a target for modulation and, accordingly, for therapeutic intervention in a range of disease
30 processes.

WO 2005/021515

PCT/IB2004/002804

The initial observation that xanthine derivatives, theophylline and caffeine inhibit the hydrolysis of cAMP led to the discovery of the required hydrolytic activity in the cyclic nucleotide phosphodiesterase (PDE) enzymes. More recently, distinct classes of PDE have been recognized, and their selective inhibition has led to improved drug therapy. Thus, it was
5 recognized that inhibition of PDE IV could lead to inhibition of inflammatory mediator release and airway smooth muscle relaxation.

3-aryl-2-isoxazoline derivatives are known as anti-inflammatory agents and isoxazoline compounds are known as inhibitors of TNF release. However, there remains a need for new selective inhibitors of phosphodiesterase (PDE) type IV.

10 Summary of Invention

The present invention provides isoxazoline derivatives, which can be used for the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult
15 respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases, and the processes for the synthesis of these compounds.

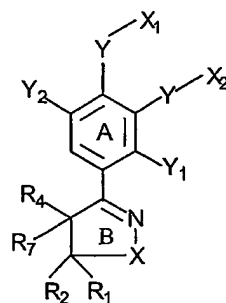
Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides of these compounds having the same type of activity are also provided.

20 Pharmaceutical compositions containing the compounds, which may also contain pharmaceutically acceptable carriers or diluents, can be used for the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome, eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other
25 inflammatory diseases.

The present invention encompasses a compound having the structure of Formula I,

WO 2005/021515

PCT/IB2004/002804



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides, wherein

X can be oxygen;

5 R_1 can be hydrogen; alkyl; heterocyclyl; $(CH_2)_{1-4} OR'$, provided that R_2 also is $(CH_2)_{1-4} OR'$; $-C(=O)NR_xR_y$, provided that R_2 also is $-C(=O)NR_xR_y$; or $-(CH_2)_m-C(=O)R_3$;

R_2 can be $-(CH_2)_mC(=O)R_3$; $-(CH_2)_{1-4} OR'$, provided R_1 also is $(CH_2)_{1-4} OR'$; $-C(=O)NR_xR_y$ provided R_1 also is $-C(=O)NR_xR_y$, or R_1 and R_2 together forms an optionally substituted cycloalkyl or heterocyclyl ring wherein the optional substituent is oxo, alkyl, 10 alkenyl, alkynyl, halogen, nitro, $-NH_2$, $-C(=O)NR_xR_y$, $-NHCOOR_6$, cyano, hydroxy, alkoxy, or substituted amino;

R_4 can be hydrogen; alkyl; $-OR_5$; halogen; $-NH_2$, substituted amino; cyano; carboxy; or $-C(=O)NR_xR_y$; or R_2 and R_4 forms an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s) 15 selected from the group consisting of N, O and S, wherein the substituents is one or more of alkyl, halogen, hydroxy, alkoxy, $-NH_2$ or substituted amino, with the proviso that R_2 and R_4 together does not form $-CH_2-O-CH_2-O-CH_2-$;

R_7 can be hydrogen, alkyl, alkenyl, alkynyl, $-OR_5$, halogen, cyano, $-NH_2$ or substituted amino;

WO 2005/021515

PCT/IB2004/002804

X_1 and X_2 each independently can be hydrogen, alkyl, alkaryl, cycloalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl;

Y can be an oxygen atom; a sulphur atom; or $-NR$;

Y_1 and Y_2 each independently can be hydrogen; alkyl; $-OR$; $-SR$; or $-NHR$;

5 wherein any of Y_1 and X_2 & X_1 and Y_2 together optionally form a cyclic ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms such as N, O and S;

X_1 and X_2 can together optionally forms a cyclic ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms such as N, O and S,

10 wherein the halogen can be F, Cl, Br, or I; R' can be alkyl, alkenyl, alkynyl, saturated or unsaturated cycloalkyl, aryl, heterocyclyl or heteroaryl; R_x and R_y each independently can be hydrogen, alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, cycloalkyl, $-SO_2R_5$, aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl; m can be an integer between 0-2; R_3 can be optionally substituted R_p or R_q ; R_6 can be
15 alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclylalkyl; and R can be hydrogen, acyl, aryl, or alkyl; and

 wherein R_5 can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl; R_p can be heterocyclyl or heteroaryl ring, wherein the rings are attached to
20 $(CH_2)_mC(=O)$ through N, and R_q can be heterocyclyl or heteroaryl ring wherein the said rings are attached to $-(CH_2)_mC(=O)$ through C.

 In some embodiments, Y can be oxygen or $-NR$; Y_1 and Y_2 are each independently hydrogen, alkyl or $-OR$. X_1 and X_2 are each independently methyl, ethyl, butyl, propyl, isopropyl, isobutyl, morpholinylmethyl, difluoromethyl, cyclopropylmethyl, cyclopentyl,
25 cyclohexyl, cycloheptyl, indanyl, adamantyl and benzyl. In another embodiment, X and Y each independently can be oxygen, X_1 and X_2 are independently optionally substituted alkyl,

WO 2005/021515

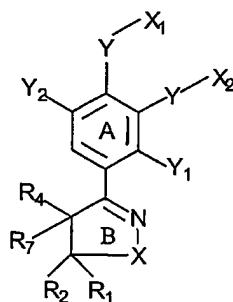
PCT/IB2004/002804

cycloalkyl, heterocyclalkyl or alkaryl; R_1 and R_2 each independently can be alkyl or $-(CH_2)_mC(=O)R_3$, wherein R_3 is R_p , or R_1 and R_2 can together join to form optionally substituted cycloalkyl and heterocycl ring; and Y_1 , Y_2 , R_4 and R_7 are each hydrogen.

R_p can be an optionally substituted heterocycl ring selected from piperazinyl, piperidinyl, pyrrolidinyl, homopiperazinyl, or diaza-bicycloheptane. In another embodiment, X_1 and X_2 can together form a cycloalkyl ring selected from the group consisting of cyclohexyl, cyclobutyl and cyclopentyl; or a heterocycl ring selected from the group consisting of tetrahydrofuran, piperidine, pyrrolidine and tetrahydropyranyl. The optional substituents on R_1 and R_2 can be $-NH_2$, difluorophenylaminocarbonyl, dichlorophenylaminocarbonyl, indanedione, tertbutylcarbamate, carboxy, tert-butoxycarbonyl or chlorophenylsulphonamidocarbonyl.

In another embodiment, X_1 and X_2 may together form a cyclic ring fused with the ring A containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms such as N, O and S.

The present invention also encompasses a compound having the structure of Formula I,



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides, wherein

X can be NR_7 or S ;

WO 2005/021515

PCT/IB2004/002804

R₇ can be hydrogen or (C₁-C₆)-alkyl;

R₁ and R₂ each independently can be alkyl; alkenyl; alkynyl; alkoxy; hydroxy; cyano; nitro; halogen; heteroaryl; heterocyclyl; heteroarylalkyl; heterocyclalkyl; -NH₂; substituted amino; carboxy; -(CH₂)_m(C=O)R₃; -C(=O)NR_xR_y; or -(CH₂)₁₋₄OR', or R₁ and R₂ may
5 together form optionally substituted cycloalkyl or heterocycl ring wherein the substituents of such a joint R₁-R₂ ring(s) can be oxo, alkyl, alkenyl, alkynyl, halogen, nitro, -NH₂, -C(=O)NR_xR_y, -NHCOOR₆, cyano, hydroxy, alkoxy, or substituted amino;

R₄ can be hydrogen; alkyl; halogen; -OR₅; cyano; carboxy; -NH₂, substituted amino, or -C(=O)NR_xR_y, or R₂ and R₄ may together form an optionally substituted 4-12 membered
10 saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatoms, wherein the heteroatom is N, O or S, with the proviso that R₂ and R₄ together does not form -CH₂-O-CH₂-O-CH₂-, and wherein the substituents is one or more of alkyl, halogen, hydroxy, alkoxy, or amino;

R₇ can be hydrogen, alkyl, alkenyl, alkynyl, -OR₅, halogen, cyano, -NH₂ or
15 substituted amino;

X₁ and X₂ each independently can be alkyl, cycloalkyl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclalkyl;

Y can be an oxygen atom; a sulphur atom; or -NR;

Y₁ and Y₂ each independently can be hydrogen; alkyl; -OR; -SR; or -NHR;

20 any of Y₁ and X₂ & X₁ and Y₂ optionally together form a cyclic ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms selected from the group consisting of N, O and S; and

X₁ and X₂ can optionally together form a cyclic ring fused with the ring A shown in Formula I, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms
25 selected from the group consisting of N, O and S;

WO 2005/021515

PCT/IB2004/002804

wherein the halogen can be F, Cl, Br, or I; R_3 can be optionally substituted R_p or R_q ; R_6 can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclalkyl; R can be hydrogen, acyl, aryl or alkyl; m can be an integer between 0-2; R_3 can be optionally substituted R_p or R_q ; R' can be alkyl, alkenyl, alkynyl, saturated or unsaturated cycloalkyl, aryl, heterocyclalkyl or heteroaryl; and R_x and R_y each independently can be hydrogen, alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, cycloalkyl, $-SO_2R_5$, aryl, alkaryl, heteroaryl, heterocyclalkyl, heteroarylalkyl, and heterocyclalkyl;

wherein R_5 can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclalkyl or heterocyclalkyl; R_p can be heterocyclalkyl or heteroaryl ring, wherein the rings are attached to $(CH_2)_mC(=O)$ through N, and R_q can be heterocyclalkyl or heteroaryl ring wherein the said rings are attached to $-(CH_2)_mC(=O)$ through C.

The present invention further encompasses a compound which is selected from:

[3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(4-carboxylic acid tert butyl-ester-piperazin-1-yl-carbonyl)-4,5-dihydroisoxazol-5-yl]-({4-carboxylic-acid-tert butyl ester piperazine-1-yl) ethanone (Compound No. 1),

1-{1-[5-(4-Acetyl-4-phenyl-piperidine-1-carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazole-5-yl]-4-acetyl-4-phenyl-piperidin-4-yl]-ethanone (Compound No. 2),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-pyrrolidin-1-yl-ethanone (Compound No. 3)

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-piperidin-1-yl-ethanone (Compound No. 4),

3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(pyrrolidin-2-carboxylic acid methyl ester-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-[pyrrolidine-2-carboxylic acid methyl ester-5-yl] ethanone (Compound No 5),

[5-[4-(4-Chlorophenyl)-4-hydroxy-piperidine-1-carbonyl]-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazol-5-yl]-[4-(4-chlorophenyl)-4-hydroxy-piperidin-1-yl]-ethanone (Compound No.6),

WO 2005/021515

PCT/IB2004/002804

- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(hydroxymethyl-piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-(4-hydroxymethyl-piperidin-1-yl)-ethanone (Compound No. 7),
- 5 [5-(5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-(carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-,5-dihydro-isoxazol-5-yl]-5-benzyl-2,5-diazabicyclo-[2.2.1]hept-2-yl-ethanone (Compound No 8),
- 10 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperidin-1-yl-methanone (Compound No. 9),
- 4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester (Compound No. 10),
- 15 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-carbonyl]-pyrrolidin-2-carboxylic acid (Compound No. 11),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester (Compound No. 12),
- 20 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-yl]-pyrrolidin-1-yl-methanone (Compound No. 13),
- [1-4]-Bipiperidiny-1-yl-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 14),
- 25 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-4-phenyl-piperidine-4-yl}-ethanone (Compound No.15),
- 30 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-methyl-piperazin-1-yl)-methanone (Compound No. 16),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperazin-1-yl-methanone (Compound No.17),
- 35 [4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5- dihydroisoxazol-5-yl]-methanone (Compound no. 18),
- {4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-[1,4]diazepan-1-yl}-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 19),
- 40 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-cyclopropylmethyl-piperazin-1-yl)-methanone (Compound No. 20)
- 45

WO 2005/021515

PCT/IB2004/002804

- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-isobutyl-1-piperazin-1-yl)-methanone (Compound No.21),
- 5 [3-Hydroxymethyl-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 22),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-hydroxy-piperidin-1-yl)-methanone (Compound No 23),
- 10 (4-Benzyl-piperidin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No 24),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperidin-4-one (Compound No. 25),
- 15 [4-(4-Bromophenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No 26),
- (5-Benzyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 27)
- 20 (4-Benzyl-piperazin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 28),
- 25 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-pyrrolidin-2-carboxylic acid methyl amide (Compound No. 29),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-pyrrolidine-2-carboxylic acid diethyl amide (Compound No. 30),
- 30 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(2-hydroxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 31),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonyl]-piperidine-2-carboxylic acid methyl ester (Compound No. 32)
- 35 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carboxyl]-pyrrolidine-2-carboxylic acid amide (Compound No. 33),
- 40 3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-bicyclo[2.2.1]heptan-2-one(Compound No. 34),
- 3-[3-Cyclopentyloxy-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-en-6-one(Compound No. 35),

WO 2005/021515

PCT/IB2004/002804

3-[3-Cyclopentyloxy-4-methoxy-phenyl]-7-methyl-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-6,9-dione (Compound No. 36),

5 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl-(2-methoxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 37)

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 38),

10 3-(3-Cyclopropylmethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 39),

3-(4-Difluoromethoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 40),

15 3-(4-Difluoro-3-butoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 41),

3-(4-Difluoromethoxy-3-isobutoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 42),

20 3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 43),

3-(3-Benzoyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 44),

25 3-(4-Difluoromethoxy-3-cyclopentyloxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 45),

30 3-(3,4-Bis-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 46),

3-(3-Butoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 47),

35 3-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 48),

40 3-(4-Difluoromethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 49),

3-(4-Benzoyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 50),

45

WO 2005/021515

PCT/IB2004/002804

- 3-(3-Cycloheptyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 51),
- 4-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 52),
- 3-[3-(indan-2-yloxy)-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 53)
- 3-(4-Ethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 54),
- 3-(3-Methoxy-4-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 55),
- 3-(4-Isopropoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 56),
- 3-(4-Butoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 57),
- 3-(4-Cyclopentyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 58),
- 3-(4-(Isobutoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 59),
- 3-(4-Cyclohexyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 60),
- 3-(4-Cyclopropylmethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 61),
- 3-(3,4-Dimethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 62),
- 3-(3-Ethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 63),
- 3-(4-Methoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 64),
- 3-(3-Isopropoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 65),
- 3-(3-Butoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 66),

WO 2005/021515

PCT/IB2004/002804

- 3-(3-Isobutoxy-4-methoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 67),
- 5 3-[4-Methoxy-3-(3-methyl-butoxy)-phenyl]-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 68),
- 3-(3-Cyclohexyloxy-4-methoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 69),
- 10 3-(3-Cycloheptyloxy-4-methoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 70),
- 3-[4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 71),
- 15 3-(3-Benzoyloxy-4-methoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 72),
- 5-(1,7-Dioxa-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 73),
- 20 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid isopropyl ester (Compound No. 74),
- Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene (Compound No. 75),
- 25 4-Chloro-N-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carbonyl]-benzene sulfonamide (Compound No. 76),
- 30 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid-(2,6-difluoro-phenyl)-amide (Compound No. 77),
- 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid-(2,4-dichloro-phenyl)-amide (Compound No. 78),
- 35 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-carbamic acid isopropyl ester (Compound No. 79),
- Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-ylamine (Compound No. 80),
- 40 2-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-isoindole-1,3-dione (Compound No. 81),
- 45 7-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-oxa-6-aza-spiro[3.4]oct-6-ene (Compound No. 82),

WO 2005/021515

PCT/IB2004/002804

PCT/IB2004/002804

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-ene
(Compound No. 83),

5 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-7-
carboxylic acid tert-butyl ester (Compound No. 84),

10 Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-
spiro[4.4]non-2-ene (Compound No. 85).

The present invention also encompasses a pharmaceutical composition comprising a
therapeutically effective amount of a compound of the present invention, together with a
pharmaceutically acceptable carrier, excipient or diluent.

15 The present invention also encompasses a method of treating AIDS, asthma, arthritis,
bronchitis, chronic obstructer pulmonary disease (COPD), psoriasis, allergic rhinitis, shock,
atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic
granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis or other inflammatory
diseases in an animal or human comprising administering to said animal or human a
therapeutically effective amount of a compound of the present invention.

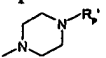
20 The present invention further encompasses a method of preventing, inhibiting or
suppressing inflammatory condition in an animal or human comprising administering to said
animal or human a therapeutically effective amount of a compound of the present invention.

The present invention encompasses a method for preparing a compound of Formula
XI, its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers,
25 diastereomers or N-oxides wherein the method comprises the steps of:

- a. reacting a compound of Formula II with hydroxylamine hydrochloride in the
presence of an acetate to form a compound of Formula III;
- b. reacting the compound of Formula III with a compound of Formula IV to form
a compound of Formula V;
- 30 c. hydrolyzing the compound of Formula V to form a compound of Formula VI;

WO 2005/021515

PCT/IB2004/002804

- d. reacting the compound of Formula VI with a compound of Formula VII, wherein Rp is , to form a compound of Formula IX; or reacting the compound of Formula VI with thionyl chloride to give a compound of Formula VIII, which can be reacted with a compound of Formula VII to form a compound of Formula IX;
- e. deprotecting the compound of Formula IX to form Formula X; and
- f. reacting the compound of Formula X with Hal-Rp', wherein Rp' is alkyl or acyl and Hal is halogen, to form a compound of Formula XI.

Preferably, the acetate is sodium acetate. In one embodiment, the compound of Formula V can be hydrolyzed in the presence of basic hydrolyzing agent. In another embodiment, the basic hydrolyzing agent is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide and a mixture thereof. In another embodiment, the compound of Formula VI can be reacted with the compound of Formula VII in the presence of a condensing agent and in the presence of a base. In yet another embodiment, the condensing agent is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide, dicyclohexyl carbodiimide and a mixture thereof, and the base is selected from the group consisting of 1,8-diazabicyclo[5.4.0]undec-7-ene, N-methylmorpholine, triethylamine, diisopropylamine, pyridine, and a mixture thereof. In another embodiment, the compound of Formula IX can be deprotected in the presence of a deprotecting agent, such as, for example, trifluoro acetic acid. In another embodiment, the compound of Formula VIII can be reacted with a compound of Formula VII in the presence of a base, such as, for example, triethylamine, diisopropylethylamine, pyridine, and a mixture thereof.

2. The present invention encompasses a method for preparing a compound of Formula XV or Formula XVI and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:

- a. reacting a compound of Formula III with a compound of Formula XII to form a compound of Formula XIII;

WO 2005/021515

PCT/IB2004/002804

- b. hydrolyzing the compound of Formula XIII to form a compound of Formula XIV; and
 - c. reacting the compound of Formula XIV with a compound of Formula VII to form a compound of Formula XVI, or
- 5 reacting the compound of Formula XIV with methylamine to form a compound of Formula XVI.

In one embodiment, the hydrolysis of the compound of Formula XIII can be carried out in the presence of a basic hydrolyzing agent, such as, for example, sodium hydroxide, lithium hydroxide, potassium hydroxide, and a mixture thereof. In another embodiment, the

10 reacting of the compound of Formula XIV with the compound of Formula VII can be carried out in the presence of an organic base, such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene, N-methylmorpholine, diisopropylamine, pyridine, and a mixture thereof, and a condensing agent, such as, for example, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride, dicyclohexylcarbodiimide, and a mixture thereof.

15 The present invention also encompasses a method for preparing a compound of Formula XVIII and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of reacting a compound of Formula III with a compound of Formula XVII to form a compound of Formula XVIII.

20 The present invention also encompasses a method for preparing a compound of Formula XXI and a compound of Formula XXII and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of reacting a compound of Formula XIX with a compound of Formula XX, wherein R_z can be alkyl optionally substituted with halogen, to form a compound of Formula XXI and a compound of Formula XXII.

25 In one embodiment, the reaction of the compound of Formula XIX with the compound of Formula XX can be carried out in the presence of a phase transfer catalyst, such as, for example, benzyl triethyl ammonium chloride.

WO 2005/021515

PCT/IB2004/002804

The present invention further encompasses a method of preparing a compound of Formula XXXI and a compound of XXXII and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:

- 5 a. reacting a compound of Formula XXII, wherein R_z is alkyl optionally substituted with halogen, with a compound of Formula of XXIII, wherein R_{z1} is alkyl, alkaryl, or cycloalkyl, to form a compound of Formula XXIV;
- b. reacting the compound of Formula XXIV with hydroxylamine hydrochloride to form a compound of Formula XXV;
- 10 c. reacting the compound of Formula XXV with a compound of Formula XXVI, wherein P is alkyl or alkaryl, to form a compound of Formula XXVII;
- d. hydrolyzing the compound of Formula XXVII to form a compound of Formula XXVIII;
- e. reducing the compound of Formula XXVIII to form a compound of Formula
15 XXIX;
- f. cyclization of the compound of Formula XXIX to form a compound of Formula XXX; and
- g. debenzylation of the compound of Formula XXX to form the compound of
20 Formula XXXI, wherein R_z is benzyl and R_{z1} is alkyl optionally substituted with halogen, or debenzylation of the compound of Formula XXX to form the compound of Formula XXXII, wherein R_z is benzyl and R_{z1} is alkyl or cycloalkyl.

In one embodiment, the reaction of a compound of Formula XXII with a compound of Formula XXIII can be carried out in the presence of a base, such as, for example, potassium
25 carbonate, sodium carbonate, sodium bicarbonate, and a mixture thereof. In another embodiment, the compound of Formula XXVII can be hydrolysed in the presence of a base,

WO 2005/021515

PCT/IB2004/002804

such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and a mixture thereof. In yet another embodiment, the compound of Formula XXVIII can be reduced in the presence of a reducing agent, such as, for example, sodium borohydride, sodium cyanoborohydride, and a mixture thereof. In one embodiment, the compound of

5 Formula XXIX undergoes cyclisation in the presence of a catalyst, such as, for example, triphenylphosphine, tri-tertbutyl phosphine, tri-cyclohexyl phosphine, and a mixture thereof.

In another embodiment, the compound of Formula XXX can be debenzylated to form the compound of Formula XXXI, wherein R_{Z1} is benzyl and R_Z is alkyl optionally substituted with halogen, or Formula XXXII, wherein R_{Z1} is benzyl and R_Z is alkyl or cycloalkyl, in the

10 presence of a deprotecting agent, wherein the deprotecting agent is palladium on carbon.

The present invention also encompasses a method of preparing a compound of Formula XXXIIa and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of debenzylation of a compound of Formula XXXII to form a compound of Formula XXXIIa, wherein Z_3 is benzyl and R_Z is

15 alkyl or cycloalkyl.

In one embodiment, the debenzylation of the compound of Formula XXXII can be carried out in the presence of a deprotecting agent or under hydrogenation transfer conditions, including hydrogen and palladium on carbon and under ammonium formate and palladium on carbon.

20 The present invention also encompasses a method of preparing a compound of Formula XXXIV and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of reacting a compound of Formula XXXI with a compound of Formula XXXIII to form a compound of Formula XXXIV.

25 In one embodiment, the reaction of a compound of Formula XXXI with a compound of Formula XXXIII can be carried out in the presence of base, such as, for example, potassium carbonate, sodium carbonate, sodium bicarbonate, and a mixture thereof.

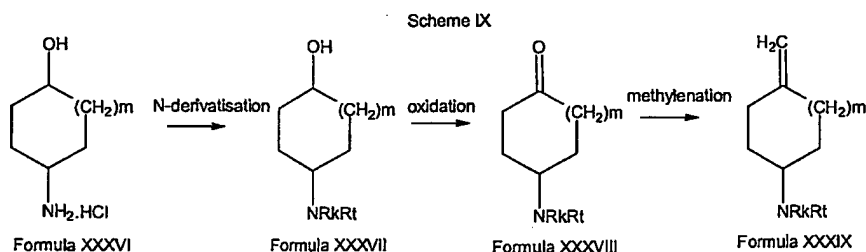
WO 2005/021515


PCT/IB2004/002804

The present invention further encompasses a method of preparing a compound of Formula XXXV and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of reacting a compound of Formula XXXIIa with a compound of Formula XXXIII to form a compound of Formula XXXV.

In one embodiment, the reaction of a compound of Formula XXXIIa with a compound of Formula XXXIII can be carried out in the presence of a base, such as, for example, potassium carbonate, sodium carbonate, sodium bicarbonate, and a mixture thereof.

The present invention encompasses a method of preparing a compound of formula XXXIX and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:



- a. N-derivatization of a compound of Formula XXXVI to form a compound of Formula XXXVII, wherein Rk is hydrogen and Rt is $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$ or Rk and Rt together joins to form ;
- b. oxidation of the compound of Formula XXXVII to form a compound of Formula XXXVIII, wherein and Rt is $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$; and
- c. methylenation of the compound of Formula XXXVIII to form a compound of Formula XXXIX.

In one embodiment, the compound of Formula XXXVI can be N-derivatised to form a compound of Formula XXXVII with tert-butyl dicarbonate and in the presence of a base,

WO 2005/021515

PCT/IB2004/002804

wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, and a mixture thereof.

In one embodiment, the compound of Formula XXXVI can be N-derivatised to form a compound of Formula XXXVII (wherein R_k) with phthalic anhydride in an organic solvent.

- 5 In another embodiment, the compound of Formula XXXVI can be N-derivatised to give a compound of Formula XXXVII in the presence of a base selected from the group consisting of triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, and a mixture thereof. In yet another embodiment, the oxidation of a compound of Formula XXXVII can be carried out in the presence of an oxidizing agent, wherein the oxidizing agent is selected from
- 10 the group consisting of pyridinium chlorochromate, manganese dioxide, potassium permanganate, Jones reagent (CrO₃/H₂SO₄), and a mixture thereof.

- In another embodiment, the methylenation of a compound of Formula XXXVIII can be carried out in the presence of Wittig salt, wherein the Wittig salt is selected from the group consisting of triphenylmethylphosphonium iodide, triphenylmethylphosphonium bromide,
- 15 and a mixture thereof.

The present invention also encompasses a method of preparing a compound of Formula XLII and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:

- a. reacting a compound of Formula XL with a compound of Formula XXV to
- 20 form a compound of Formula XLI; and
- b. deprotecting the compound of Formula XLI to form a compound of Formula XLII.

- In one embodiment, the reaction of a compound of Formula XL with a compound of Formula XXV can be carried out in the presence of a base, wherein the base is selected from
- 25 the group consisting of pyridine, N-methylmorpholine, triethylamine, diisopropylethylamine, and a mixture thereof.

WO 2005/021515

PCT/IB2004/002804

The present invention also encompasses a method of preparing a compound of Formula L and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:

- a. N-protecting a compound of Formula XLIII to form a compound of Formula XLIV;
5 XLIV;
- b. oxidizing the compound of Formula XLIV to form a compound of Formula XLV;
- c. methylenation of the compound of Formula XLV to form a compound of Formula XLVI;
- 10 d. reacting the compound of Formula XLVI with a compound of Formula XXV to form a compound of Formula XLVII;
- e. deprotecting the compound of Formula XLVII to form a compound of Formula XLVIII; and
- f. reacting the compound of XLVIII with a compound of Formula XLIX to form
15 a compound of Formula L.

In one embodiment, the N-protection of the compound of Formula XLIII can be carried out in the presence of a base, wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, and a mixture thereof.

20 In another embodiment, the oxidation of a compound of Formula XLIV can be carried out using an oxidizing agent, wherein the oxidizing agent is selected from the group consisting of pyridinium chlorochromate, manganese dioxide, potassium permanganate, Jones reagent ($\text{CrO}_3/\text{H}_2\text{SO}_4$), and a mixture thereof.

In yet another embodiment, the methylenation of a compound of Formula XLV can be carried out in the presence of a Wittig salt, wherein the Wittig salt is selected from the group

WO 2005/021515

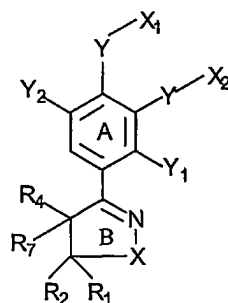
PCT/IB2004/002804

consisting of triphenylmethyl- phosphonium iodide, triphenylmethylphosphonium bromide, and a mixture thereof.

In another embodiment, the reaction of a compound of Formula XLVI with a compound of Formula XXV can be carried out in the presence of a base, wherein the base is
5 selected from the group consisting of pyridine, N-methylmorpholine, diisopropylethylamine, triethylamine, and a mixture thereof.

Detailed Description of the Invention

In accordance with one aspect, the present invention encompasses a compound having the structure of Formula I



Formula I

10

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein

X can be oxygen;

R_1 can be hydrogen; alkyl; heterocyclyl; $(CH_2)_{1-4} OR'$, provided that R_2 is also
15 $(CH_2)_{1-4} OR'$; or $-C(=O)NR_xR_y$ provided that R_2 is also $-C(=O)NR_xR_y$; $-(CH_2)_m-C(=O)R_3$;

R_2 can be $-(CH_2)_mC(=O)R_3$; $-(CH_2)_{1-4} OR'$, provided R_1 is also $(CH_2)_{1-4}OR'$;
 $-C(=O)NR_xR_y$ provided R_1 is also $-C(=O)NR_xR_y$; or R_1 and R_2 may together form optionally
substituted cycloalkyl or heterocyclyl ring wherein the substituents of such a joint R_1 - R_2
ring(s) can be oxo, alkyl, alkenyl, alkynyl, halogen (e.g., F, Cl, Br, or I), nitro, $-NH_2$, -
20 $C(=O)NR_xR_y$, $-NHCOOR_6$, cyano, hydroxy, alkoxy, or substituted amino;

R_4 can be hydrogen; alkyl; $-OR_5$; halogen (e.g., F, Cl, Br, or I); $-NH_2$, substituted amino; cyano; carboxy; or $-C(=O)NR_xR_y$, or R_2 and R_4 may together form optionally

WO 2005/021515

PCT/IB2004/002804

substituted 4-12 membered (un)saturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s) selected from N, O and S with the proviso that R₂ and R₄ together does not form -CH₂-O-CH₂-O-CH₂-, wherein the substituents can be one or more of alkyl, halogen (e.g., F, Cl, Br, or I), hydroxy, alkoxy, -NH₂ or substituted amino;

5 R₇ can be hydrogen, alkyl, alkenyl, alkynyl, -OR₅, halogen (e.g., F, Cl, Br, I), cyano, -NH₂ or substituted amino;

X₁ and X₂ each independently can be hydrogen, alkyl, alkaryl, cycloalkyl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

Y can be an oxygen atom; a sulphur atom; or -NR;

10 Y₁ and Y₂ independently can be hydrogen; alkyl; -OR; -SR; or -NHR;

any of Y₁ and X₂ & X₁ and Y₂ may together form a cyclic ring fused with the ring A shown in Formula I, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms, such as N, O and S; and

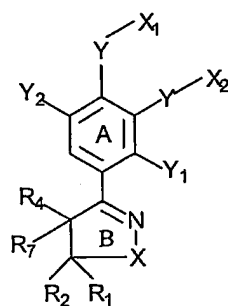
15 X₁ and X₂ can together form a cyclic ring fused with the ring A shown in Formula I, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms, such as N, O and S,

wherein R' can be alkyl, alkenyl, alkynyl, (un)saturated cycloalkyl, aryl, heterocyclyl or heteroaryl; R_x and R_y can be hydrogen, alkyl, alkenyl of three to six carbon atoms, alkynyl of three to six carbon atoms, cycloalkyl, -SO₂R_s, aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl; m can be an integer in the range of 0-2; R₃ can be optionally substituted R_p or R_q, wherein R_p can be heterocyclyl or heteroaryl ring wherein the said rings are attached to (CH₂)_mC(=O) through N, and R_q can be heterocyclyl or heteroaryl ring, wherein the said rings can be attached to -(CH₂)_mC(=O) through C; R₆ can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclylalkyl; R can be hydrogen, acyl, aryl, or alkyl; 20 and R_s can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl.

In accordance with another aspect, the present invention encompasses a compound having the structure of Formula I

WO 2005/021515

PCT/IB2004/002804



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein

X can be NR₇ or S, wherein R₇ can be hydrogen or (C₁-C₆)-alkyl, *i.e.*, lower alkyl;

5 R₁ and R₂ each independently can be alkyl; alkenyl; alkynyl; alkoxy; hydroxy; cyano; nitro; halogen (*e.g.*, F, Cl, Br, I); heteroaryl; heterocyclyl; heteroarylalkyl; heterocyclalkyl; -NH₂; substituted amino; carboxy; -(CH₂)_m(C=O)R₃; -C(=O)NR_xR_y; or -(CH₂)₁₋₄OR'; or R₁ and R₂ may together form optionally substituted cycloalkyl or heterocyclyl ring wherein the substituents of such a joint R₁-R₂ ring(s) can be oxo, alkyl, alkenyl, alkynyl, halogen (*e.g.*, F, Cl, Br, I), nitro, -NH₂, -C(=O)NR_xR_y, -NHCOOR₆, cyano, hydroxy, alkoxy or substituted amino;

15 R₄ can be hydrogen; alkyl; halogen (*e.g.*, F, Cl, Br, I); -OR₅; cyano; carboxy; -NH₂; substituted amino; or -C(=O)NR_xR_y; or R₂ and R₄ may together form optionally substituted 4-12 membered (un)saturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s), such as N, O and S, with the proviso that R₂ and R₄ together does not form -CH₂-O-CH₂-O-CH₂-, wherein the substituents can be one or more of alkyl, halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkoxy, or amino;

R₇ can be hydrogen, alkyl, alkenyl, alkynyl, -OR₅, halogen (*e.g.*, F, Cl, Br, I), cyano, -NH₂ or substituted amino;

20 X₁ and X₂ each independently can be alkyl, cycloalkyl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclalkyl;

Y can be an oxygen atom; a sulphur atom; or -NR;

Y₁ and Y₂ each independently can be hydrogen; alkyl; -OR; -SR; or -NHR;

WO 2005/021515

PCT/IB2004/002804

any of Y_1 and X_2 & X_1 and Y_2 may together form a cyclic ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms, such as N, O and S; and

X_1 and X_2 may together form a cyclic ring fused with the ring A, the ring containing
5 3-5 carbon atoms within the ring and having 2-3 heteroatoms, such as N, O and S,

wherein m can be an integer in the range of 0-2; R_3 can be optionally substituted R_p or R_q , wherein R_p can be heterocyclyl or heteroaryl ring wherein the said rings are attached to $(CH_2)_mC(=O)$ through N, and R_q can be heterocyclyl or heteroaryl ring, wherein the said rings can be attached to $-(CH_2)_mC(=O)$ through C; R_x
10 and R_y can be hydrogen, alkyl, alkenyl of three to six carbon atoms, alkynyl of three to six carbon atoms, cycloalkyl, $-SO_2R_5$, aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl; R' can be alkyl, alkenyl, alkynyl, (un)saturated cycloalkyl, aryl, heterocyclyl or heteroaryl; R_6 can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclylalkyl; R_5 can be hydrogen, alkyl,
15 alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl; R can be group hydrogen, acyl, aryl or alkyl;

The following definitions apply to terms as used herein.

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon having from 1 to about 20 carbon atoms. This term is
20 exemplified by groups, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, tetradecyl, and the like. The alkyl groups may be further substituted with one or more substituents such as alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryloxy, aminosulfonyl,
25 aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, $-S(O)_nR_5$ (wherein n can be 0, 1 or 2 and R_5 can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl), heterocyclyl or heteroaryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, aminocarbonyl, hydroxy, alkoxy, halogen,
30 $-CF_3$, amino, substituted amino, cyano, and $-S(O)_nR_5$ (wherein n and R_5 are the same as defined earlier) or an alkyl group as defined above that is interrupted by 1-5 atoms or groups

WO 2005/021515

PCT/IB2004/002804

independently chosen from oxygen, sulfur and $\text{-NR}_a\text{-}$ (where R_a can be hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, or aryl). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3 , amino, substituted amino, cyano, and $\text{-S(O)}_n\text{R}_5$ (wherein n and R_5 are the same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 20 carbon atoms with cis or trans geometry. Preferred alkenyl groups include ethenyl or vinyl (CH=CH_2), 1-propylene or allyl ($\text{-CH}_2\text{CH=CH}_2$), or iso-propylene ($\text{-C(CH}_3\text{)=CH}_2$), bicyclo[2.2.1]heptene, and the like. In the event that the alkenyl is attached to a heteroatom, the double bond cannot be alpha to the heteroatom. The alkenyl group may be further substituted with one or more substituents, such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxy-carbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, $\text{-S(O)}_n\text{R}_5$ (wherein n and R_5 are the same as defined earlier), heterocyclyl or heteroaryl. Unless otherwise constrained by the definition, all substituents may be optionally further substituted by 1-3 substituents, which can be alkyl, carboxy, aminocarbonyl, hydroxy, alkoxy, halogen, -CF_3 , amino, substituted amino, cyano, or $\text{-S(O)}_n\text{R}_5$ (wherein R_5 and n are the same as defined earlier).

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2 to 20 carbon atoms. Preferred alkynyl groups include ethynyl, (-C=CH), or propargyl (or propynyl, $\text{-CH}_2\text{C=CH}$), and the like. In the event that the alkynyl is attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. The alkynyl group may be further substituted with one or more substituents, such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxy-carbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, or $\text{-S(O)}_n\text{R}_5$ (wherein R_5 is the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be optionally further

WO 2005/021515

PCT/IB2004/002804

substituted by 1-3 substituents, which can be alkyl, carboxy, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃, amino, substituted amino, cyano, or -S(O)_nR₅ (wherein R₅ and n are the same as defined earlier).

The term "cycloalkyl," unless otherwise specified, refers to saturated or unsaturated cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which contains an optional olefinic bond. Such cycloalkyl groups include, by way of example, single ring structures, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, cyclopropylene, cyclobutylene and the like, or multiple ring structures, such as adamantanyl, and bicyclo [2.2.1]heptane, or cyclic alkyl groups to which is fused an aryl group, for example, indane and the like. The cycloalkyl may be further substituted with one or more substituents such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, -S(O)_nR₅ (wherein R₅ is the same as defined earlier), heteroaryl or heterocyclyl. Unless otherwise constrained by the definition, all substituents may be optionally further substituted by 1-3 substituents, which can be alkyl, carboxy, aminocarbonyl, hydroxy, alkoxy, halogen, CF₃, -NH₂, substituted amino, cyano, or -S(O)_nR₅ (wherein R₅ and n are the same as defined earlier).

The term "alkoxy" denotes the group O-alkyl, wherein alkyl is the same as defined above.

The term "alkaryl" refers to alkyl-aryl linked through alkyl portion (wherein alkyl is the same as defined earlier) and the alkyl portion contains carbon atoms from 1-6 and aryl is same as defined below.

The term "aryl," unless otherwise specified, refers to phenyl or naphthyl ring, and the like, optionally substituted with 1 to 3 substituents selected from the group consisting of halogen (such as F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, aryloxy, -S(O)_nR₅ (wherein R₅ is the same as defined earlier), cyano, nitro, carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, acyl and (CH₂)₀₋₃C(=O)NR_xR_y (wherein R_x and R_y are same as defined earlier).

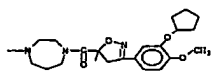
WO 2005/021515

PCT/IB2004/002804

The term "carboxy," unless otherwise specified, refers to $-C(=O)O-R_6$, wherein R_6 can be, for example, hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclalkyl.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure
 5 containing 5 or 6 carbon atoms, or a bicyclic aromatic group having 8 to 10 carbon atoms, with one or more heteroatom(s) independently selected from the group consisting of N, O and S, optionally substituted with 1 to 3 substituent(s), such as halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, $-S(O)_nR_5$ (wherein n and R_5 are the same as defined earlier), alkoxy, alkaryl, cyano, nitro, acyl or $C(=O)NR_xR_y$ (wherein R_x and R_y are the same
 10 as defined earlier). Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, and the like, including analogous oxygen, sulphur, and mixed hetero atom containing groups.

The term "heterocycl," unless otherwise specified, refers to a saturated or
 15 unsaturated monocyclic or polycyclic ring having 5 to 10 atoms, in which 1 to 3 carbon atoms in a ring are replaced by heteroatoms selected from the group consisting of O, S and N, and optionally are benzofused or fused heteroaryl of 5-6 ring members and/or optionally are substituted, wherein the substituents can be halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, hydroxyalkyl, cycloalkyl, carboxy, aryl, alkoxy, alkaryl, heteroaryl, heterocycl,
 20 heteroarylalkyl, heterocyclalkyl, oxo, alkoxyalkyl or $-S(O)_nR_5$ (wherein n and R_5 are the same as defined earlier), cyano, nitro, $-NH_2$ substituted amino, acyl or $-C(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier). Examples of heterocycl groups include, but are not limited to, tetrahydrofuranyl, dihydrofuranyl, azabicyclohexane dihydropyridinyl, piperidinyl, isoxazoline, piperazinyl, dihydrobenzofuryl, isoindole-dione, dihydroindolyl,

25  and the like.

"Heteroarylalkyl," unless otherwise specified, refers to an alkyl-heteroaryl group, wherein the alkyl and heteroaryl portions are the same as defined earlier.

"Heterocyclalkyl," unless otherwise specified, refers to an alkyl-heterocycl group, wherein the alkyl and heterocycl portions of the group are the same as defined earlier.

WO 2005/021515

PCT/IB2004/002804

The term "acyl" as defined herein refers to $-C(=O)R''$, wherein R'' is the same as defined earlier.

The term "substituted amino," unless otherwise specified, refers to a group $-N(R_k)_2$ wherein each R_k can be hydrogen [provided that both R_k groups are not hydrogen (defined as
5 "NH₂")], alkyl, alkenyl, alkynyl, alkaryl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, acyl, $S(O)_mR_5$ (wherein m and R_5 is the same as defined above), $-C(=O)NR_xR_y$, $-C(=O)OR_x$ (wherein R_x and R_y are the same as defined earlier) or $-NHC(=O)NR_yR_x$ (wherein R_y and R_x are the same as defined earlier).

Unless otherwise constrained by the definition, all substituents optionally may be
10 further substituted by 1-3 substituents, which can be alkyl, alkaryl, cycloalkyl, aryl, heteroaryl, heterocyclyl, carboxy, hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-C(=O)NR_xR_y$, $-O(C=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier) and $-OC(=O)NR_xR_y$, or $-S(O)_mR_5$ (where R_5 is the same as defined above and m is 0, 1 or 2).

The compounds of the present invention can be used for treating AIDS, asthma,
15 arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, shock, atopic dermatitis, crohn's disease, adult respiratory distress syndrome, eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases. Accordingly, the present invention encompasses a method of treating AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis,
20 shock, atopic dermatitis, crohn's disease, adult respiratory distress syndrome, eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis or other inflammatory diseases, which comprises administering to a patient in need thereof a therapeutically effective amount of an isoxazoline derivative compound of the present invention, and particularly an isoxazoline derivative compound of the present invention together a
25 pharmaceutically acceptable carrier, excipient or diluent.

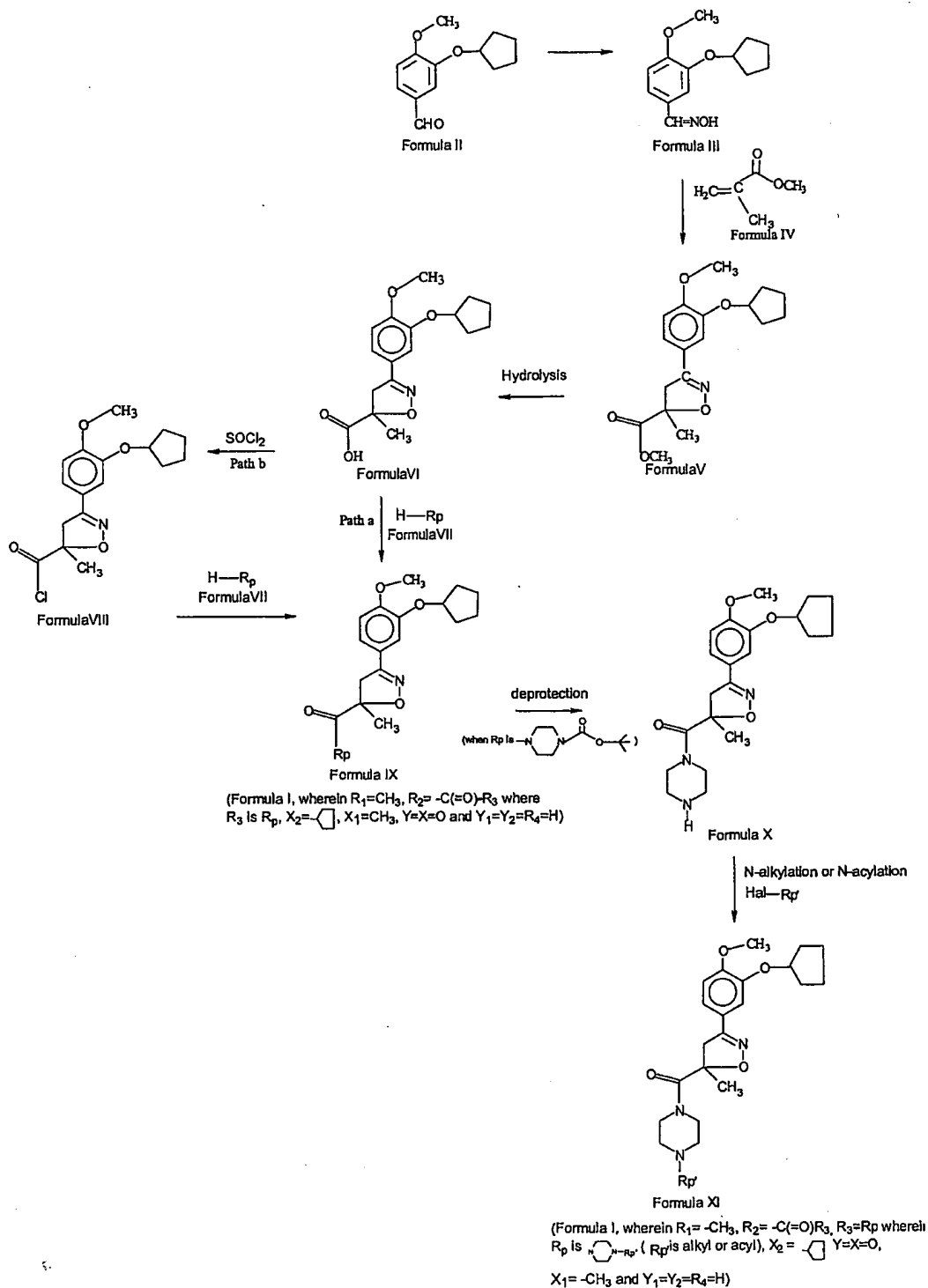
In accordance with yet another aspect, there are provided processes for the preparation of the compounds as described herein.

The compounds of the present invention may be prepared by techniques well known in the art. In addition, the compounds of the present invention may be prepared following a
30 reaction sequence as depicted below.

WO 2005/021515

PCT/IB2004/002804


Scheme I



WO 2005/021515

PCT/IB2004/002804

Compounds of Formula XI can be prepared by methods shown in Scheme I. Thus, a compound of Formula II is reacted with hydroxylamine hydrochloride in the presence of an acetate, such as sodium acetate, to yield the compound of Formula III, which can be further reacted with a compound of Formula IV to give a compound of Formula V, which can be hydrolysed to give a compound of Formula VI.

A compound of Formula VI (Path a) can be condensed with a compound of Formula VII to give a compound of Formula IX (Formula I, wherein $R_1 = CH_3$, $R_2 = -C(=O)R_3$ wherein R_3 can be R_p , Y and X can be O, X_2 can be cyclopentyl ring, X_1 can be $-CH_3$, and Y_1 , Y_2 , and R_4 can be H), which can be deprotected to give a compound of Formula X, which can be N-alkylated or acylated with a compound of Formula Hal- R_p' (wherein R_p' can be alkyl or acyl, for example, *t*-butylcarbonyl, and Hal is halogen) to furnish a compound of Formula XI (Formula I, R_1 can be $-CH_3$, R_2 can be $-C(=O)R_3$ where R_3 is R_p (R_p is , X_2 can be cyclopentyl ring, X_1 can be $-CH_3$ and Y_1 , Y_2 , and R_4 can be H).

Alternatively, a compound of Formula VI can be reacted with thionyl chloride (Path b) to give a compound of Formula VIII, which can be condensed with a compound of Formula VII to give a compound of Formula IX (Formula I, wherein R_1 can be CH_3 , R_2 can be $-C(=O)R_3$, wherein R_3 can be R_p , Y and X can be O, X_2 can be cyclopentyl ring, X_1 can be $-CH_3$ and Y_1 , Y_2 and R_4 can be H).

The reaction of compound of Formula III with a compound of Formula IV to give a compound of Formula V can be carried out in an organic solvent, such as, for example, tetrahydrofuran, dimethylformamide or dimethylsulphoxide. The hydrolysis of compound of Formula V to give a compound of Formula VI can be carried out in the presence of a basic hydrolyzing agent, such as, for example, sodium hydroxide, lithium hydroxide or potassium hydroxide. Alternatively, the hydrolysis of compound of Formula V to give a compound of Formula VI also can be carried out in the presence of acidic hydrolyzing agents, such as, for example dilute sulphuric acid, dilute hydrochloric acid or acetic acid.

The hydrolysis of compound of Formula V to give a compound of Formula VI can be carried out in an organic solvent, such as, for example, methanol, ethanol, propanol or isopropyl alcohol. The condensation of compound of Formula VI (Path a) with a compound of Formula VII to give a compound of Formula IX can be carried out in the presence of a

WO 2005/021515

PCT/IB2004/002804

condensing agent, such as, for example, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC·HCl) or dicyclohexyl carbodiimide (DCC).

The condensation of compound of Formula VI with a compound of Formula VII to give a compound of Formula IX can be carried out in the presence of a base, such as, for example 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), N-methylmorpholine (NMM), triethylamine, diisopropylethylamine or pyridine. The condensation of compound of Formula VI with a compound of Formula VII to give a compound Formula IX can be carried out in an organic solvent, such as, for example, dimethyl formamide, dimethylsulphoxide or tetrahydrofuran.

The compound of Formula IX can be deprotected to give a compound of Formula X with deprotecting agent, such as, for example, trifluoroacetic acid and in an organic solvent, such as, for example, dichloromethane, dichloroethane, chloroform or carbon tetrachloride. The compound of Formula X can be N-alkylated or acylated with a Compound of Formula Hal-R_p to give compound Formula XI in an organic solvent, such as, for example, dry acetone.

The compound of Formula VI (Path b) can be reacted with thionyl chloride to give a compound of Formula VIII in an organic solvent, such as, for example, dichloromethane, chloroform or carbon tetrachloride. The compound of Formula VIII can be condensed with a compound of Formula VII to give a compound of Formula IX in an organic solvent, such as, for example, tetrahydrofuran, dimethylformamide, or dimethylsulphoxide. The compound of Formula VIII can be condensed with a compound of Formula VII to give a compound of Formula IX in an organic base, such as, for example, triethylamine, diisopropylamine or pyridine.

Typical compounds prepared following the procedure as described in Scheme I, Path a include:

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperdin-1-yl-methanone (Compound No. 9),

4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester (Compound No. 10),

WO 2005/021515

PCT/IB2004/002804

- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-carbonyl]-pyrrolidin-2-carboxylic acid (Compound No. 11),
- 5 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester (Compound No. 12),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-yl]-pyrrolidin-1-yl-methanone (Compound No. 13),
- 10 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-4-phenyl-piperidine-4-yl}-ethanone (Compound No.15),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-methyl-15 piperazin-1-yl)-methanone (Compound No. 16),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]- piperazin-1-yl-methanone (Compound No.17),
- 20 [4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5- dihydroisoxazol-5-yl]-methanone (Compound no. 18),
- {4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-[1,4]diazepan-1-yl}-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-25 5-yl]-methanone (Compound No. 19),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-cyclopropylmethyl-piperazin-1-yl)-methanone (Compound No. 20),
- 30 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-isobutyl-1-piperazin-1-yl)-methanone (Compound No.21),

WO 2005/021515

PCT/IB2004/002804

[3-Hydroxymethyl-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 22),

- 5 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-hydroxy-piperidin-1-yl)-methanone (Compound No 23),

(4-Benzyl-piperidin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No 24),

10

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperidin-4-one (Compound No. 25),

- 15 [4-(4-Bromophenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No 26),

(5-Benzyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-hydroxy-piperidin-1-yl)-methanone (Compound No. 27),

20

(4-Benzyl-piperazin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 28),

- 25 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-pyrrolidin-2-carboxylic acid methyl amide (Compound No. 29),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonyl]-pyrrolidine-2-carboxylic acid diethyl amide (Compound No. 30),

- 30 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(2-hydroxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 31),

WO 2005/021515

PCT/IB2004/002804

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonyl]-piperidine-2-carboxylic acid methyl ester (Compound No. 32),

- 5 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carboxyl]-pyrrolidine-2-carboxylic acid amide (Compound No. 33), and

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl-(2-methoxy methyl-pyrrolidin-1-yl)-methanone (Compound No. 37).

10

Typical compounds prepared following the procedure as described in Scheme I, Path b include:

- 15 [1-4]-Bipiperidinyl-1-yl-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4-,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 14).

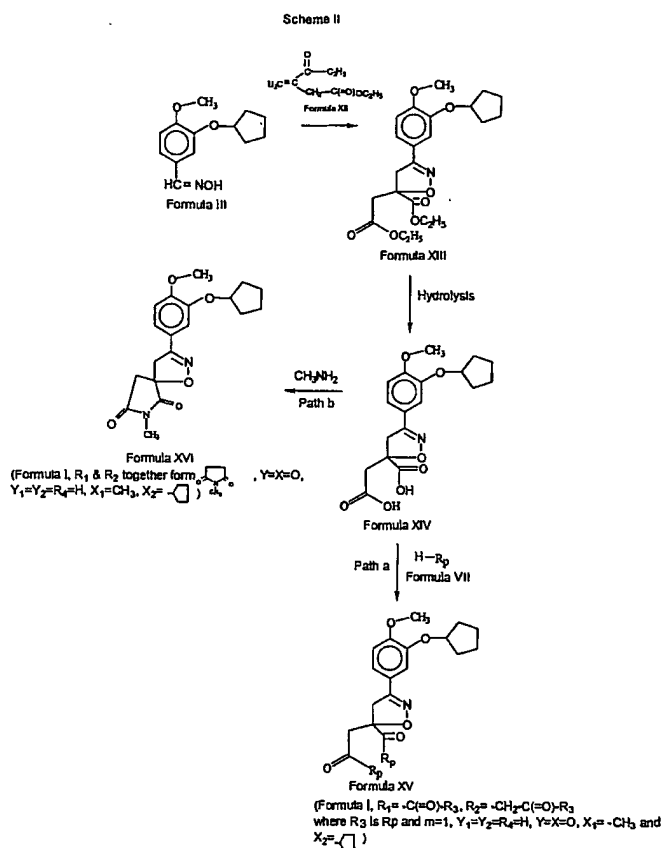
- Compounds of Formula XV can also be prepared by following the reaction sequence of Scheme II. Thus, a compound of Formula III can be reacted with a compound of Formula XII to give a compound of Formula XIII, which can be further hydrolysed to give a
- 20 compound of Formula XIV. The compound of Formula XIV (Path a) either can be condensed with a compound of Formula VII to furnish a compound of Formula XV (Formula I, wherein R_1 can be CH_3 , R_2 can be $-CH_2-C(=O)R_3$, wherein R_3 can be R_p , X and Y can be O, X_1 can be CH_3 , X_2 can be cyclopentyl, and Y_1 , Y_2 and R_4 can be H) in the presence suitable condensing agent and a suitable organic base or the compound of Formula XIV (Path b) is reacted with
- 25 methylamine to furnish a compound of Formula XVI (Formula I, R_1 and R_2 together form



, Y and X can be O, Y_1 , Y_2 and R_4 can be H, X_1 can be CH_3 , X_2 can be cyclopentyl).

WO 2005/021515

PCT/IB2004/002804



The reaction of compound of Formula III with compound of Formula XII to give a compound of Formula XIII can be carried out in an organic solvent, such as, for example, tetrahydrofuran, dimethylformamide or dimethylsulphoxide. The hydrolysis of compound of Formula XIII to give a compound of Formula XIV can be carried out in the presence of a basic hydrolyzing agent, such as, for example sodium hydroxide, lithium hydroxide or potassium hydroxide. The hydrolysis of compound of Formula XIII to give a compound of Formula XIV can be carried out in a suitable organic solvent, such as, for example methanol, ethanol, propanol or isopropyl alcohol.

Alternatively, hydrolysis of compound of Formula XIII to give a compound of Formula XIV can be carried out in the presence of a suitable acidic hydrolyzing agent, such as, for example, dilute sulfuric acid, dilute hydrochloric acid or acetic acid. The condensation of compound of Formula XIV with the compound of Formula VII (Path a) to give a compound of Formula XV can be carried out in the presence of a condensing agent, such as,

WO 2005/021515

PCT/IB2004/002804

for example, 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride (EDCHCl),
dicyclohexyl carbodiimide (DCC). The condensation of compound of Formula XIV with the
compound of Formula VII to give a compound of Formula XV can be carried out in the
presence of an organic base, such as, for example 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),

5 N-methylmorpholine, triethylamine, diisopropylamine or pyridine.

The condensation of compound of Formula XIV with the compound of Formula VII to
give a compound of Formula XV can be carried out in an organic solvent, such as, for
example, tetrahydrofuran, dimethylsulphoxide or dimethylformamide. The condensation of
compound of Formula XIV with amino methyl (Path b) to give a compound of Formula XVI
10 can be carried out in an organic solvent, such as, for example, tetrahydrofuran,
dimethylsulphoxide or dimethylformamide.

The compounds prepared following the procedure as described in Scheme II Path a
include:

15 [3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(4-carboxylic acid tert butyl-ester-piperazin-1-yl-
carbonyl)-4,5-dihydroisoxazol-5-yl)-({4-carboxylic-acid-tert butyl ester piperazine-1-yl) —,
ethanone (Compound No. 1),

1-{1-[5-(4-Acetyl-4-phenyl-piperidine-1-carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-
20 4,5-dihydro-isoxazole-5-yl]-4-acetyl-4-phenyl-piperidin-4-yl]-ethanone (Compound No. 2),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-5-
yl]-pyrrolidin-1-yl-ethanone (Compound No. 3),

25 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-
yl]-piperidin-1-yl-ethanone (Compound No. 4),

3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(pyrrolidin-2-carboxylic acid methyl ester-1-
carbonyl)-4,5-dihydro-isoxazol-5-yl)-[pyrrolidine-2-carboxylic acid methyl ester-5-yl]
30 ethanone (Compound No 5),

WO 2005/021515

PCT/IB2004/002804

[5-[4-(4-Chlorophenyl)-4-hydroxy-piperidine-1-carbonyl]-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazol-5-yl]-[4-(4-chlorophenyl)-4-hydroxy-piperidin-1-yl]-ethanone (Compound No.6),

- 5 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(hydroxymethyl-piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-(4-hydroxymethyl-piperidin-1-yl)-ethanone (Compound No. 7), and

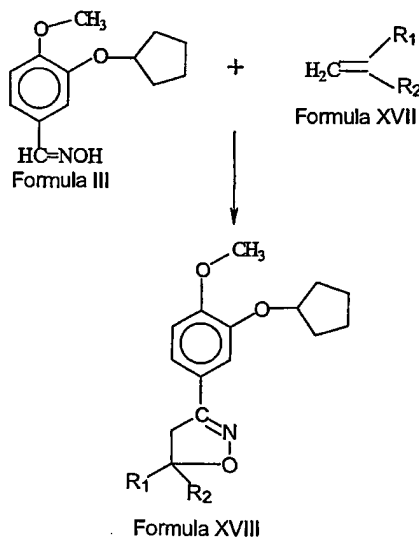
[5-(5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-(carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-,5-dihydro-isoxazol-5-yl]-5-benzyl-2,5-diazabicyclo-[2.2.1]hept-2-yl-ethanone

- 10 (Compound No 8).

The compounds prepared following the procedure as described in Scheme II Path b include:

- 15 3-[3-Cyclopentyloxy-4-methoxy-phenyl]-7-methyl-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-6,9-dione (Compound No. 36).

Scheme III



(Formula I where R₁ and R₂ together forms a monocyclic or bicyclic ring system having 0-4 heteroatoms optionally substituted by one or more oxo, Y = X=O, X₁=CH₃, X₂ = cyclopentyl ring, Y₁=Y₂=R₄=H)

WO 2005/021515

PCT/IB2004/002804

Compounds of Formula I can also be prepared by following the reaction sequence of Scheme III. Thus, the compound of Formula III can be reacted with the compound of Formula XVII to give a compound of Formula XVIII (Formula I, wherein R₁ and R₂ together form a monocyclic or bicyclic ring system having 0-4 heteroatoms optionally substituted by one or more of oxo, X and Y can be O, X₁ can be CH₃, X₂ can be cyclopentyl ring, Y₁, Y₂, and R₄ can be H).

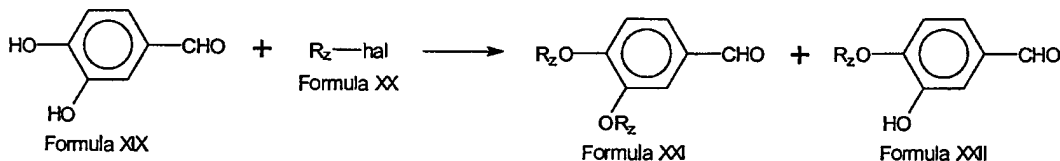
The reaction of compound of Formula III with a compound of Formula XVII to give a compound of Formula XVIII can be carried out in an organic solvent, such as, for example tetrahydrofuran, dimethylformamide or dimethylsulphoxide.

The compounds prepared following the procedure as described in Scheme III include:

3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-bicyclo[2.2.1]heptan-2-one(Compound No. 34), and

3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-en-6-one(Compound No. 35).

Scheme IV



Compounds of Formulae XXI and XXII can also be prepared by following the reaction sequence of Scheme IV. Thus, the compound of Formula XIX can be reacted with a compound of Formula XX (wherein R₂ represents alkyl optionally substituted with halogen) to give a compound of Formula XXI and XXII.

The compound of Formula XIX can be reacted with a compound of Formula XX to give compounds of Formulae XXI and XXII in an organic solvent, such as, for example dimethylformamide, tetrahydrofuran, dioxane or diethylether in the presence of a phase transfer catalyst, such as, for example, benzyl triethylammonium chloride.

WO 2005/021515

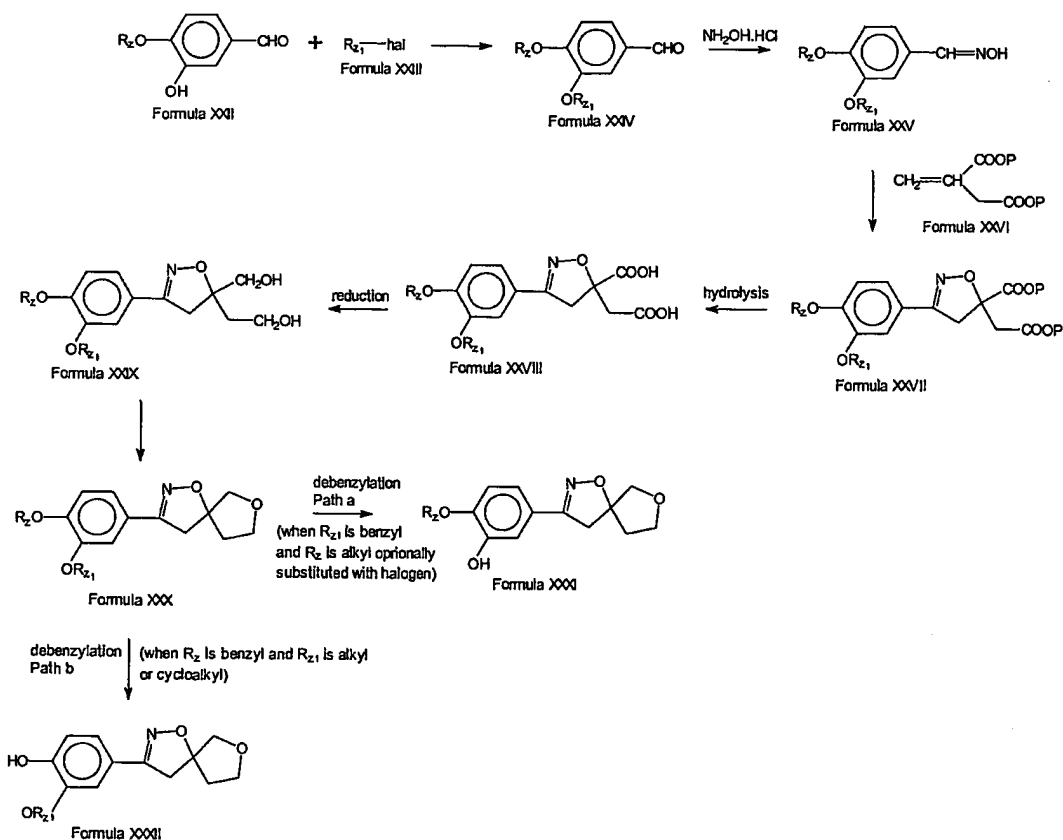
PCT/IB2004/002804

The compounds prepared following the procedure as described in Scheme IV include:

4-Difluoromethoxy-3-hydroxy-benzaldehyde, and

5 3,4-Bis-difluoromethoxy-benzaldehyde.

Scheme V



Compounds of Formulae XXX and XXXI can be prepared by following the reaction sequence of Scheme V. Thus, the compound of Formula XXII (wherein R₂ is the same as defined earlier) can be reacted with a compound of Formula XXIII (wherein R₂₁ can be alkyl, alkaryl or cycloalkyl) to give a compound of Formula XXIV, which can be reacted with hydroxyl amine hydrochloride to give a compound of Formula XXV, which can be reacted

WO 2005/021515

PCT/IB2004/002804

with a compound of Formula XXVI (wherein P can be alkyl or alkaryl) to give a compound of Formula XXVII, which can undergo hydrolysis to give a compound of Formula XXVIII, which can undergo reduction to give a compound of Formula XXIX, which can undergo ring cyclisation to give a compound of Formula XXX, which can undergo debenzylation to give a compound of Formula XXXI.

The reaction of compound of Formula XXII with a compound of Formula XXIII to give a compound of Formula XXIV can be carried out in an organic solvent, such as, for example, dimethylformamide, tetrahydrofuran, diethylether or dioxane, in the presence of base, such as, for example, potassium carbonate, sodium carbonate or sodium bicarbonate.

The compound of Formula XXIV can be reacted with hydroxyl amine hydrochloride to give a compound of Formula XXV in an organic solvent, such as, for example, ethanol, methanol, propanol or isopropyl alcohol. The compound of Formula XXV can be reacted with a compound of Formula XXVI to give a compound of Formula XXVII in an organic solvent, such as, for example, tetrahydrofuran, dimethylformamide, dioxane or diethylether. The hydrolysis of a compound of Formula XXVII to give a compound of Formula XXVIII can be carried out in a solvent system, such as, for example, tetrahydrofuran, methanol, dioxane or ethanol, in water in the presence of base, such as, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide. The compound of Formula XXVIII can undergo reduction to give a compound of Formula XXIX in an organic solvent, such as, for example, tetrahydrofuran, dimethylformamide, dioxane or diethyl ether, with reducing agent, such as, for example, sodium borohydride or sodium cyanoborohydride. The compound of Formula XXIX can undergo ring cyclisation to give a compound of Formula XXX in an organic solvent, such as, for example tetrahydrofuran, dimethylformamide, dioxane or diethyl ether, with reagents, such as, for example, diisopropyldiazadicarboxylate (DIAD) or diethyldiazadicarboxylate (DEAD), in the presence of catalyst, such as, for example, triphenyl phosphine, tri-tertbutyl phosphine or tricyclohexyl phosphine. The compound of Formula XXX can be debenzylated (when R₂₁ can be benzyl) to give a compound of Formula XXXI in an organic solvent, such as, for example, methanol, ethanol, propanol or isopropylalcohol, with a deprotecting agent, such as, for example, palladium on carbon.

The compounds prepared following the procedure as described in Scheme V include:

WO 2005/021515

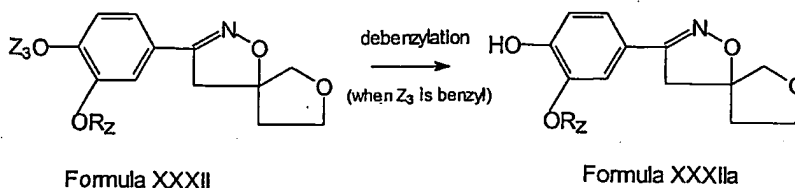
PCT/IB2004/002804

- 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 38),
- 3-(3-Cyclopropylmethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
5 (Compound No. 39),
- 3-(4-Difluoromethoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 40),
- 10 3-(4-Difluoro-3-butoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 41),
- 3-(4-Difluoromethoxy-3-isobutoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 42),
- 15 3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 43),
- 3-(3-Benzoyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 44),
20 3-(4-Difluoromethoxy-3-cyclopentyloxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 45),
- 3-(3,4-Bis-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 46),
25 46),
- 3-(3-Benzoyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 72), and
- 30 5-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 73).

WO 2005/021515

PCT/IB2004/002804

Scheme VI



The compound of Formula XXXIIa can be prepared, for example, by reaction sequence as depicted in Scheme VI. Thus, a compound of Formula XXXII can be debenzylated (wherein Z₃ can be benzyl) to give a compound of Formula XXXIIa.

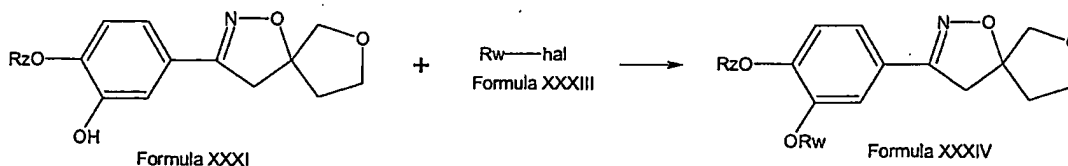
The debenzylation of a compound of formula XXXII to give a compound of formula XXXIIa can be carried out in an organic solvent, such as, for example, methanol, ethanol, propanol or isopropylalcohol, with a deprotecting agent, such as, for example, using hydrogen and palladium on carbon or under catalytic hydrogenation transfer conditions of ammonium formate and palladium on carbon.

Particular compounds formed following the procedure described in Scheme VI include:

3-(4-Benzyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 50), and

4-(1,7-dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy phenol (Compound No. 52).

Scheme VII



The compound of Formula XXXIV can be prepared by following the reaction sequence as depicted in Scheme VII. Thus, the compound of Formula XXXI can be reacted

WO 2005/021515

PCT/IB2004/002804

with a compound of Formula XXXIII (wherein R_w can be alkyl or cycloalkyl and hal can be Br, Cl or I) to give a compound of Formula XXXIV.

The reaction of a compound of Formula XXXI with a compound of Formula XXXIII to give a compound of Formula XXXIV can be carried out in an organic solvent, such as, for example, dimethylformamide, tetrahydrofuran, diethylether or dioxane, in the presence of
5 base, such as, for example, potassium carbonate, sodium carbonate or sodium bicarbonate.

Particular compounds formed following the procedure shown in Scheme VII include:

3-(3-Butoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
10 No. 47),

3-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-
2-ene (Compound No. 48),

15 3-(4-Difluoromethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 49),

3-(3-Cycloheptyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 51),
20

3-[3-(indan-2-yloxy)-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 53)

25 3-(3,4-Dimethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 62),

3-(3-Ethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 63),

3-(4-Methoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 64),

30 3-(3-Isopropoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No.
65),

WO 2005/021515

PCT/IB2004/002804

3-(3-Butoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 66),

3-(3-Isobutoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 67),

5

3-[4-Methoxy-3-(3-methyl-butoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 68),

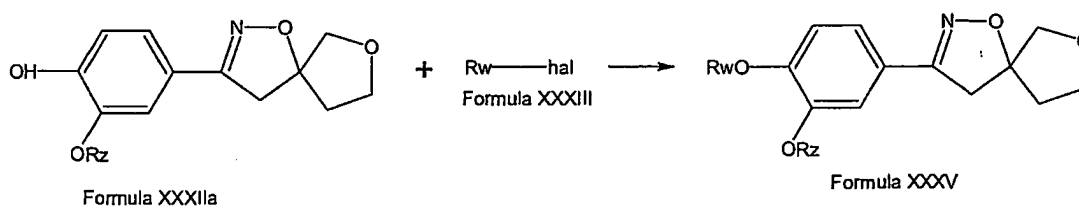
3-(3-Cyclohexyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 69),

3-(3-Cycloheptyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 70),

15 3-[4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 71), and

5-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 73).

Scheme VIII



The compound of Formula XXXV can be prepared by following the reaction sequence as depicted in Scheme VIII. Thus, a compound of Formula XXXIIa can be reacted with a compound of Formula XXXIII to give a compound of Formula XXXV.

25 The reaction of a compound of Formula XXXIIa with a compound of Formula XXXIII to give a compound of Formula XXXV can be carried out in an organic solvent, such

WO 2005/021515

PCT/IB2004/002804

as, for example, dimethylformamide, tetrahydrofuran, diethyl ether or dioxane, in the presence of a base, such as, for example, potassium carbonate, sodium carbonate or sodium bicarbonate.

Particular compounds formed following the procedure shown in Scheme VIII include:

5

3-(4-Ethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 54),

3-(3-Methoxy-4-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 55),

10 3-(4-Isopropoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 56),

3-(4-Butoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 57),

15 3-(4-Cyclopentyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 58),

3-(4-(Isobutoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 59),

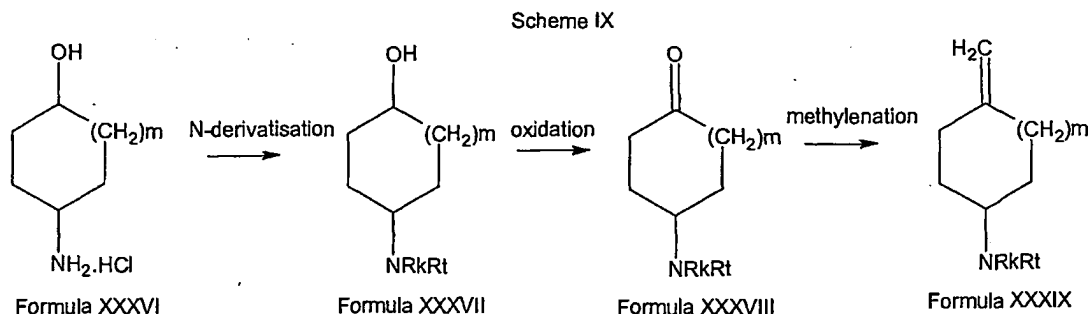
20


3-(4-Cyclohexyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 60), and

25 3-(4-Cyclopropylmethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 61).


WO 2005/021515

PCT/IB2004/002804



The compound of Formula XXXIX can be prepared by following the reaction sequence as depicted in Scheme IX. Thus, a compound of Formula XXXVI (wherein m can be 0 or 1) undergoes N-derivatization to give a compound of Formula XXXVII (wherein Rk can be hydrogen and Rt can be $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$ or Rk and Rt together with nitrogen joins to form ) which can be oxidized to give a compound of Formula XXXVIII, which can further undergo methylenation reaction to give a compound of Formula XXXIX.

The compound of Formula XXXVI can be N-derivatised to give a compound of Formula XXXVII [wherein Rk can be hydrogen and Rt can be $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$] with tert-butyl dicarbonate in an organic solvent, such as, for example, dichloromethane, carbon tetrachloride or chloroform, in the presence of a base, such as, for example, triethylamine, diisopropylethylamine, N-methylmorpholine or pyridine.

The compound of Formula XXXVI can be N-derivatised to give a compound of Formula XXXVII (when Rk and Rt together joins to form ) with phthalic anhydride in an organic solvent, such as, for example toluene, dioxane, diethyl ether or benzene, in the presence of a base, such as, for example, triethylamine, diisopropylethylamine, N-methylmorpholine or pyridine.

The oxidation of a compound of Formula XXXVII to give a compound of Formula XXXVIII can be carried out using an oxidizing agent, such as, for example, pyridinium chlorochromate, manganese dioxide, potassium permanganate or Jones reagent ($\text{CrO}_3/\text{H}_2\text{SO}_4$).

The methylenation of a compound of Formula XXXVIII to give a compound of Formula XXXIX can be carried out in an organic solvent, such as, for example, tetrahydrofuran, dimethylformamide, dioxane or diethylether, in the presence of Wittig salt,

WO 2005/021515

PCT/IB2004/002804

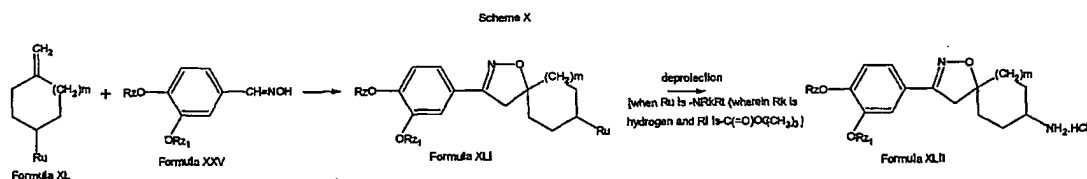
such as, for example, triphenylmethylphosphonium iodide or triphenylmethylphosphonium bromide.

Alternatively, the methylenation of a compound of Formula XXXVIII to give a compound of Formula XXXIX can be carried out using $\text{Zn}/\text{CH}_2\text{Br}_2/\text{TiCl}_4$ in an organic solvent, such as, for example tetrahydrofuran, dimethylformamide, dioxane or diethylether.

Particular compounds formed following the procedure shown in Scheme IX include:

4-(methylene-cyclohexyl)-carbamic acid tert-butyl ester, and

2-(4-methylene-cyclohexyl)-isoindole-1,3-dione.



The compound of Formula XLII can be prepared by following the reaction sequence as depicted in Scheme X. Thus, a compound of Formula XL (wherein m can be 0 or 1 and Ru can be -NR_kR_t or no atom) can be reacted with a compound of Formula XXV to give a compound of Formula XLI, which can be deprotected [wherein Ru can be -NR_kR_t, wherein R_k can be hydrogen and R_t can be -C(=O)OC(CH₃)₃] to give a compound of Formula XLII.

The reaction of a compound of Formula XL with a compound of Formula XXV to give a compound of Formula XLI can be carried out in an organic solvent, such as, for example, chloroform, dichloromethane, carbon tetrachloride or dichloroethane, in the presence of a base, such as, for example, pyridine, N-methylmorpholine, triethylamine or diisopropylethylamine.

The deprotection of a compound of Formula XLI to give a compound of Formula XLII [wherein Ru can be -NR_kR_t, wherein R_k can be hydrogen and R_t can be -C(=O)OC(CH₃)₃] can be carried out in an organic solvent, such as, for example, methanol in hydrochloric acid or ethanol in hydrochloric acid.

Particular compounds formed following the procedure shown in Scheme X include:

WO 2005/021515

PCT/IB2004/002804

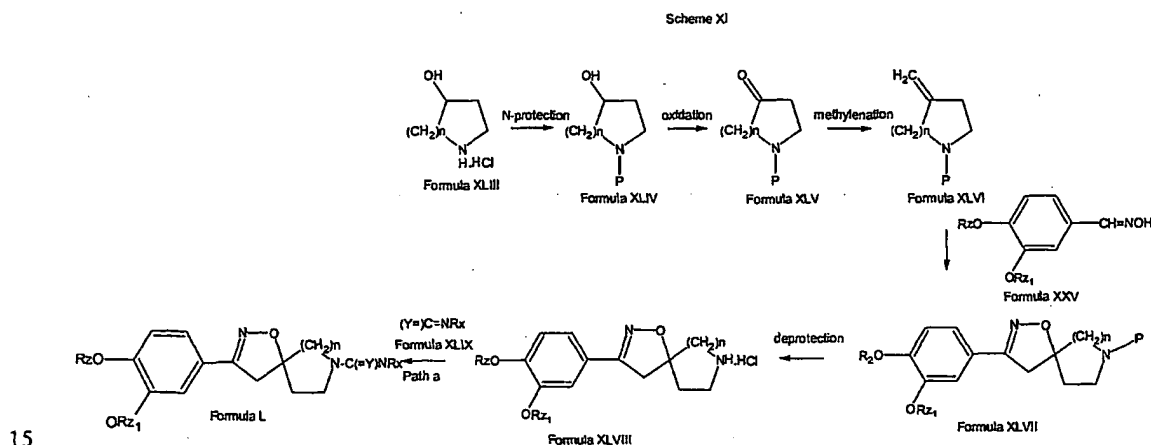
[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-carbamic acid isopropyl ester (Compound No. 79),

Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-ylamine (Compound No. 80),

2-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-isoindole-1,3-dione (Compound No. 81),

7-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-oxa-6-aza-spiro[3.4]oct-6-ene (Compound No. 82), and

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-ene (Compound No. 83).



The compounds of Formula L can be prepared by following the reaction sequence as depicted in Scheme XI. Thus, a compound of Formula XLIII (wherein n can be 1, 2 or 3) can be N-protected to give a compound of Formula XLIV (wherein P can be $-C(=O)OC(CH_3)_3$, $-C(=O)OC(CH_3)_2CHBr_2$ or $-C(=O)OC(CH_3)_2CCl_3$) to give a compound of Formula XLIV, which can be oxidized to give a compound of Formula XLV, which can undergo methylenation to give a compound of Formula XLVI, which can be reacted with a compound of Formula XXV to give a compound of Formula XLVII, which can be deprotected to give a

WO 2005/021515

PCT/IB2004/002804

compound of Formula XLVIII, which can be reacted with a compound of Formula XLIX (wherein Y can be oxygen or sulfur and Rx can be the same as defined earlier) to give a compound of Formula L.

The N-protection of a compound of Formula XLIII to give a compound of Formula XLIV [wherein P can be $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$] can be carried out in an organic solvent, such as, for example, dichloromethane, dichloroethane or carbon tetrachloride, in the presence of a base, such as, for example triethylamine, diisopropylethylamine, N-methylmorpholine or pyridine.

The N-protection of a compound of Formula XLIII to give a compound of Formula XLIV [when P can be $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CHBr}_2$ or $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CCl}_3$] can be carried out following the procedure, as described in Theodora W. Greene and Peter G.M. Wuts, "Protecting Groups In Organic Synthesis," 3rd edition, John Wiley and Sons, New York 1999.

The oxidation of a compound of Formula XLIV to give a compound of Formula XLV can be carried out using an oxidizing agent, such as, for example, pyridinium chlorochromate, manganese dioxide, potassium permanganate or Jones reagent ($\text{CrO}_3/\text{H}_2\text{SO}_4$).

The methylenation of a compound of Formula XLV to give a compound of Formula XLVI can be carried out in an organic solvent, such as, for example, tetrahydrofuran, dimethylformamide, dioxane or diethylether, in the presence of a Wittig salt for example, triphenylmethyl-phosphonium iodide or triphenylmethylphosphonium bromide.

Alternatively, the methylenation of a compound of Formula XLV to give a compound of Formula XLVI can be carried out using $\text{Zn}/\text{CH}_2\text{Br}_2/\text{TiCl}_4$ in an organic solvent, such as, for example, tetrahydrofuran, dimethylformamide, dioxane or diethylether.

The reaction of a compound of Formula XLVI with a compound of Formula XXV to give a compound of Formula XLVII can be carried out in an organic solvent, such as, for example, dichloromethane, chloroform, carbon tetrachloride or dichloromethane, in the presence of a base, such as, for example, pyridine, N-methylmorpholine, diisopropylethylamine or triethylamine.

The deprotection of a compound of Formula XLVII (wherein P can be $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$) to give a compound of Formula XLVIII can be carried out in an organic solvent, such as, for example, methanol, ethanol, propanol or isopropylalcohol, in the

WO 2005/021515

PCT/IB2004/002804

presence of an alcoholic acid solution, such as, for example, ethanolic hydrochloric acid or methanolic hydrochloric acid.

The deprotection of a compound of Formula XLVII (wherein P can be $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CHBr}_2$) can be carried out in an organic solvent, such as, for example, ethanol, methanol, propanol or isopropylalcohol, or by hydrobromide in acetic acid.

The deprotection of a compound of Formula XLVII (wherein P can be $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_2\text{CCl}_3$) can be carried out by a supernucleophile, such as, for example, lithium cobalt (I) phthalocyanine, zinc and acetic acid or cobalt phthalocyanine.

The compound of Formula XLVIII can be reacted with a compound of Formula XLIX in an organic solvent, such as, for example, dichloroethane, dichloromethane, chloroform or carbon tetrachloride, to give a compound of Formula L.

Particular compounds formed following the procedure shown in Scheme XI include:

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid isopropyl ester (Compound No. 74),

Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene (Compound No. 75),

4-Chloro-N-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carbonyl]-benzene sulfonamide (Compound No. 76),

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid-(2,6-difluoro-phenyl)-amide (Compound No. 77),

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid-(2,4-dichloro-phenyl)-amide (Compound No. 78),

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-7-carboxylic acid tert-butyl ester (Compound No. 84), and

WO 2005/021515

PCT/IB2004/002804

Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene (Compound No. 85).

In the above schemes, specific bases, condensing agents, hydrolyzing agents, solvents, and the like, known to those skilled in the art, may be used. Similarly, the reaction temperature and duration of the reaction may be adjusted according to the desired needs.

The Examples set forth below demonstrate the general synthetic procedure for the preparation of representative compounds. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the claims.

10

EXAMPLES

GENERAL PROCEDURE

15 **Synthesis of 3-Cyclopentyloxy-4-methoxy-benzaldehyde (Formula II)**

The title compound was prepared according to the method described in *J Med. Chem.*, 1994, 37, 1696-1703.

Synthesis of 3-Cyclopentyloxy-4-methoxy-benzaldehyde oxime (Formula III)

20 Hydroxylamine hydrochloride (0.473 g, 6.8181 mmol) and sodium acetate (0.56 g, 6.8181 mmol) was added to a stirred solution of compound of Formula II (0.5 g, 2.2727 mmol) in ethanol (8 mL). The reaction mixture was stirred at room temperature for 50 minutes. Ethanol was evaporated under reduced pressure, which was diluted with water (20 mL) and the organic compound was extracted with ethyl acetate (2x15 mL). The ethyl acetate
25 layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford compound of Formula III. Analysis by ¹H NMR spectroscopy gave the following peaks (CDCl₃): 9.84 (s, 1H), 8.07 (s, 1H), 6.84-7.24 (m, 3H), 4.79-4.83 (m, 1H), 3.87 (s, 3H), 1.62-2.18 (m, 8H).

30 **Synthesis of 2-(3-Cyclopentyloxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-isoxazol-5-carboxylic acid methyl ester (Formula V)**

Methyl methacrylate (42.5 g, 0.42 mol, 10 eq) was added to the solution of compound of Formula III (10 g, 0.042 mol, 1 eq) in tetrahydrofuran (70 mL), and the resulting reaction

WO 2005/021515

PCT/IB2004/002804

mixture was stirred at room temperature. Sodium hypochlorite (100 mL) was added slowly to the mixture thus obtained over the period of 20 minutes and the reaction mixture was allowed to stir at room temperature overnight. A second lot of sodium hypochlorite (100 mL) was again added to it and stirred for 2 hours at room temperature. Tetrahydrofuran was evaporated off and the organic compound was extracted with ethyl acetate twice. The organic layer was concentrated to yield the title compound with a yield of 14 g. The melting point of the compound was 107-108°C. Analysis by ¹H NMR spectroscopy gave the following peaks (CDCl₃): δ 7.38-7.39 (d, 1H), 7.02-7.06 (dd, 1H), 6.85-6.88 (d, 1H), 4.82-4.85 (m, 1H), 3.80-3.83 (s, 6H, 2xOCH₃), 3.63 (s, 1H), 3.2-3.25 (d, 1H), 1.92-2.07 (m, 8H), 1.79 (s, 3H). Mass spectroscopy gave the following peaks (m/z): 333 (M)⁺, 334.3 (M+1)⁺.

Synthesis of 2-(3-Cyclopentyloxy-4-methoxy-phenyl)-4-methyl-4,5-dihydro-isoxazol-5-carboxylic acid (Formula VI)

The compound of Formula V (0.07, 0.2102 mmole, 1 eq.) was dissolved in tetrahydrofuran (1.5 mL) and lithium hydroxide in water solution (0.48 mL of 0.5 M aqueous solution, 0.24 mmoles, 1.2 eq) was added. The mixture was stirred for 1 hour at room temperature and an additional amount of lithium hydroxide in water solution (0.19 mL, 0.5 M, 0.004 g) was added. The mixture was stirred for 2 hour 35 minutes. Solvent was removed under reduced pressure and the residue thus obtained was diluted with water and acidified with drop of concentrated hydrochloric acid. The organic compound was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulphate and finally concentrated under reduced pressure to afford title organic compound with a yield of 0.066 g, and a melting point of 142-144°C. Analysis by ¹H NMR spectroscopy gave the following peaks (C₃D₆O): 7.31-7.32 (d, 1H), 7.15-7.18 (dd, 1H), 6.69-7.00 (d, 1H) 4.85-4.87 (m, 1H), 3.83-6.89(s, 3H, OCH₃), 3.60 (s, 1H), 3.30-3.31 (d, 1H), 1.96-2.06 (m, 8H), 1.64(s, 3H, 1x CH₃). Mass spectroscopy gave the following peaks (m/z): 319 (M)⁺, 320.2 (M+1)⁺.

Synthesis of 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-ethoxycarbonylmethyl-4,5-dihydro-isoxazol-5-yl]-acetic acid ethyl ester (Formula XIII)

The compound of Formula III (3 g, 0.0127 moles, 1 eq) was dissolved in tetrahydrofuran and 2-methylene succinic acid diethyl ester (4.74g, 0.0255M) was added.

WO 2005/021515

PCT/IB2004/002804

The resulting reaction mixture was heated to 60 °C with constant stirring. Solution of sodium hypochlorite (24.0 mL) was added slowly to the mixture at 60-65 °C and stirred for 20 hours. A second amount of sodium hypochlorite (2 mL) was added to the mixture and stirred for five hours. Tetrahydrofuran was evaporated off from the reaction mixture and to the residue thus
5 obtained was added ethyl acetate (30 mL), washed with water (40 mL), dried over sodium sulphate and concentrated under reduced pressure to afford the crude organic compound. The crude compound was purified by column chromatography using ethyl acetate and hexane solvent mixture as an eluent, with a yield of 2.52 gm, and a melting point of 85-86°C. Analysis by ¹H NMR spectroscopy gave the following peaks (CDCl₃): 7.35 (s, 1H), 7.03-7.07
10 (d, 1H), 6.83-6.86 (d, 1H), 4.80-4.82 (m, 1H), 4.18-4.31 (m, 4H), 3.98-4.04 (d, 1H), 3.88 (s, 3H), 3.43-3.49 (d, 1H), 3.22-3.28 (d, 1H), 2.92-2.98 (d, 1H), 1.80-1.99 (m, 8H), 1.11-1.33 (m, 6H). Mass spectroscopy gave the following peaks (m/z): 419(M)⁺, 420.6(M+1)⁺.

**Synthesis of 5-Carboxymethyl-3-(3-cyclopentyloxy-4-methoxyphenyl)-4,5-dihydro-
15 isoxazol-5-carboxylic acid (Formula XIV)**

The title compound was prepared following the procedure as described for the synthesis of compound of Formula VI, by using compound of Formula XIII in place of compound of Formula V. Analysis by ¹H NMR spectroscopy gave the following peaks (DMSO-d₆): 6.98-7.21 (m, 3H), 4.83 (s, 1H), 3.78 (s, 3H), 3.49-3.55 (d, 1H), 2.89 (s, 2H),
20 2.50-2.73 (d, 1H), 1.70-1.99 (m, 8H). Mass spectroscopy gave the following peaks (m/z): 363 (M)⁺, 364.1 (M+1)⁺.

**Example 1: 1-{1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-
5-carbonyl]-4-phenyl-piperidine-4-yl}-ethanone (Compound No.15)**

25 Hydroxybenzotriazole (0.0296g, 0.2194 mmole) and N-methyl morpholine (48 µL, 0.4388 mmole) were added to a cooled (0-5°C) solution of compound of Formula VI (0.07 gm, 0.2194 mmole) and 1-(4-phenyl-piperidin-4-yl)-ethanone (0.0789 g, 0.3291 mmole) in 0.6 mL dry dimethyl formamide. The resulting solution was allowed to stir at 0-5 °C for 1 hour. Thereafter, dicyclohexylcarbodiimide (0.0903 g, 0.4388 mmol) was added and the
30 resulting mixture was allowed to stir at the same temperature for 30 minutes, followed by stirring at room temperature for 22.5 hours. The reaction was quenched by adding water (10 mL) to the reaction mixture. The resulting solution was extracted with ethyl acetate (2x15

WO 2005/021515

PCT/IB2004/002804

mL). The white solid, which separated on keeping the ethyl acetate layer at room temperature, was filtered off. The filtrate was dried over anhydrous sodium sulphate and was concentrated under reduced pressure to afford the title organic compound with a yield of 0.1916 g. Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 6.82-7.26(m, 8H), 4.79(s, 1H), 4.06-4.08(d, 1H), 3.86(s, 3H), 3.06-3.12(d, 1H), 1.158-1.836(m, 22H).

Particular analogs of 1-{1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-dihydro-isoxazole-5-carbonyl]-4-phenyl-piperidine-4-yl} ethanone (Compound No.15), which are described below, can be prepared by substitution of the compound of Formula VI with corresponding cyclic amines.

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-carbonyl]-pyrrolidin-2-carboxylic acid (Compound No. 11)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.32-7.33 (d, 1H), 6.99-7.07 (dd, 1H), 6.83-6.83 (d, 1H), 4.80 (s, 1H), 3.87-4.56 (m, 5H), 3.18-3.31 (m, 1H), 1.25-2.23 (m, 14H), 1.25 (s, 3H). Mass spectroscopy showed the following peaks (m/z): 416 (M) $^+$, 417 ($\text{M}+1$) $^+$.

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperidin-1-yl-methanone (Compound No. 9)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.3 (s, 1H), 7.07-7.09 (d, 1H), 6.83-6.86 (d, 1H), 4.80 (s, 1H), 3.86-3.93 (m, 7H), 3.07-3.35 (m, 2H), 1.52-2.01 (m, 17H). Mass spectroscopy showed the following peaks (m/z): 386 (M) $^+$, 387.6 ($\text{M}+1$) $^+$.

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-methyl-piperazin-1-yl)-methanone (Compound No. 16)

Analysis by ^1H NMR spectroscopy showed the following peaks: 7.26-7.32 (d, 1H), 7.06-7.09 (d, 1H), 6.83-6.86 (d, 1H), 4.78-4.81 (m, 1H), 4.32-4.38 (d, 1H), 3.87 (s, 3H), 3.08-3.14 (d, 1H), 2.35-2.53 (m, 7H), 1.58-2.04 (m, 15 H). Mass spectroscopy showed the following peaks (m/z): 401 (M) $^+$, 402.5 ($\text{M}+1$) $^+$.

WO 2005/021515

PCT/IB2004/002804

[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-methanone (Compound No. 18)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): 6.84-7.43 (m, 7H), 4.80 (s, 1H), 4.40-4.46 (d, 1H), 3.86 (s, 3H), 3.09-3.11 (1H), 1.71-2.34 (m, 19H).

5 Mass spectroscopy showed the following peaks (m/z): 512.5 (M)⁺, 513.2 (M+1)⁺.

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester (Compound No. 12)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): 7.33-7.37 (d, 1H), 7.07-7.09 (d, 1H), 6.85-6.83 (d, 1H), 4.82 (s, 1H), 4.10-4.23 (d, 1H), 3.71-3.91 (m, 6H), 3.09-3.22 (d, 1H), 1.67-2.19 (m, 18H). Mass spectroscopy showed the following peaks (m/z): 430 (M)⁺, 431.2 (M+1)⁺.

[3-Hydroxymethyl-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 22)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): 7.32 (s, 1H), 7.07-7.10 (d, 1H), 6.83-6.86 (d, 1H), 4.80 (s, 1H), 3.82 (s, 3H), 3.41-3.52 (m, 2H), 2.84 (s, 2H), 1.47-2.08 (m, 20H). Mass spectroscopy showed the following peaks (m/z): 416 (M)⁺, 417.3 (M+1)⁺.

20

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-pyrrolidin-1-yl-methanone (Compound No. 13)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): 7.32 (s, 1H), 7.05-7.08 (d, 1H), 6.83-6.85 (d, 1H), 4.80-4.81 (m, 1H), 4.17-4.23 (d, 1H), 3.79 (s, 3H), 3.11-3.16 (d, 1H), 1.63-2.01 (m, 19H). Mass spectroscopy showed the following peaks (m/z): 372 (M)⁺, 373.1. (M+1)⁺.

25

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-isobutyl-1-piperazin-1-yl)-methanone (Compound No 21)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): 7.28 (s, 1H), 7.01-7.04 (d, 1H), 6.78-6.81 (d, 1H), 4.75 (s, 1H), 4.27-4.32 (d, 1H), 3.02-3.08 (d, 1H), 3.82

30

WO 2005/021515

PCT/IB2004/002804

(s, 3H), 1.56-2.03 (m, 18H), 1.20 (s, 3H), 0.84-0.86 (m, 7H). Mass spectroscopy showed the following peaks (m/z): 443 (M)⁺, 444 (M+1)⁺.

4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-
5 piperazine-1-carboxylic acid tert-butyl ester (Compound No. 10)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): 7.26-7.32 (d, 1H), 7.07-7.09 (d, 1H), 6.84-6.86 (d, 1H), 4.79-4.81 (m, 1H), 4.32-4.38 (d, 1H), 3.09-3.15 (d, 1H), 3.78 (s, 3H, OCH₃), 1.68-1.99 (m, 16H), 1.43 (s, 9H, 3xCH₃). Mass spectroscopy showed the following peaks (m/z): 487 (M)⁺, 488.5 (M+1)⁺.

10

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-carbonyl]-
pyrrolidin-3-carboxylic acid diethyl amide (Compound No. 30)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): δ 7.320 (d, 1H) 7.047-7.078 (d, 1H), 6.828-6.849 (d, 1H) 4.816 (s, 1H) 4.80 (m, 1H), 4.25-4.31 (d, 1H),
15 3.90-3.96 (d, 1H), 3.86 (s, 3H), 3.5-3.6 (2H), 3.37-3.43 (m, 2H), 3.1-3.23 (m, 2H), 1.08-1.97 (m, 21H). Mass spectroscopy showed the following peaks (m/z): 471 (M)⁺, 472.700 (M+1)⁺.

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carboxyl]-
20 pyrrolidine-3-carboxylic acid amide (Compound No. 33)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): 7.32 (s, 1H), 7.05-7.08 (d, 1H), 6.83-6.86 (d, 1H). 4.80-4.82 (s, 1H), 4.06-4.125 (d, 1H), 3.87-3.89 (s, 3H), 3.35-3.40 (m, 2H), 3.35-3.40 (m, 1H), 2.84 (s, 3H), 1.6-2.0 (M, 13H). Mass spectroscopy showed the following peaks (m/z): 415 (m)⁺ 416.300 (M+1)⁺.

WO 2005/021515

PCT/IB2004/002804

[4-(4-Bromophenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No 26)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.342-7.49 (m, 5H), 7.09-7.11 (d, 1H), 6.84-6.87 (d, 1H), 4.81 (s, 1H), 4.40-4.46 (d, 1H), 3.88 (s, 1H), 3.09-3.21 (m, 1H), 1.68-2.17 (m, 19H). Mass spectroscopy showed the following peaks: 557 (M) $^+$, 558 (M+1) $^+$.

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperidin-4-one (Compound No. 25)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): 7.32-7.33 (d, 1H), 7.07-7.10 (d, 1H), 6.84-6.87 (d, 1H), 9.81-4.83 (m, 1H), 4.42-4.44 (d, 1H), 3.88 (s, 3H), 3.13-3.19 (d, 1H), 2.49-2.51 (m, 4H), 1.57-2.04 (m, 15H). Mass spectroscopy showed the following peaks (m/z): 400 (M) $^+$, 401.2 (M+1) $^+$.

(5-Benzyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 27)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.303-7.35 (m, 6H), 7.06-7.08 (d, 1H), 6.83-6.88 (m, 1H), 4.8 (s, 1H), 3.87 (s, 3H, OCH_3), 3.70-3.78 (m, 3H), 3.33-3.5 (m, 2H), 2.8 (s, 2H), 1.6-2.04 (m, 16H). Mass spectroscopy showed the following peaks (m/z): 489 (M) $^+$, 490.500 (M+1) $^+$.

(4-Benzyl-piperazin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 28)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.26-7.32 (m, 6H), 7.06-7.08 (d, 1H), 6.83-6.86 (d, 1H), 4.8 (s, 1H), 4.31-3.37 (d, 1H), 3.87 (s, 3H), 3.36-3.4 (m, 2H), 3.13 (d, 1H), 2.35-2.55 (m, 8H), 1.61-2.04 (m, 11H). Mass spectroscopy showed the following peaks (m/z): 477 (M) $^+$, 478.500 (M+1) $^+$.

30

WO 2005/021515

PCT/IB2004/002804

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-pyrrolidin-3-carboxylic acid methyl amide (Compound No 29)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.33 (d, 1H), 7.05-7.07 (d, 1H), 6.84-6.87 (d, 1H), 4.80-4.81 (d, 1H); 4.18-4.23 (d, 1H), 3.87 (s, 3H), 3.10-3.22 (m, 1H), 2.72-2.82 (m, 3H), 1.62-2.10 (m, 18H). Mass spectroscopy showed the following peaks (m/z) : 429 (M^+), 430.500 ($\text{M}+1$) $^+$.

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonyl]-piperidine-2-carboxylic acid methyl ester (Compound No. 32)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.33-7.35 (d, 1H), 7.07-7.10 (d, 1H), 6.83-6.86 (m, 1H), 4.79-9.8 (d, 1H), 4.36-4.42 (d, 1H), 3.8 (s, 3H), 3.71-3.79 (m, 3H), 3.0-3.16 (d, 1H), 1.23-2.04 (m, 20H). Mass spectroscopy showed the following peaks (m/z): 444(M^+), 445.5 ($\text{M}+1$) $^+$.

15 (4-Benzyl-piperidin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 24)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 6.8-7.34 (m, 8H), 4.8 (d, 1H), 4.54-4.48 (d, 1H), 9.36-4.41(d, 1H), 3.87 (s, 3H), 3.06-3.15 (m, 2H), 2.53-2.63 (m, 4H), 1.64-2.04 (m, 16H). Mass spectroscopy showed the following peaks (m/z): 476 (M^+), 477.3 ($\text{M}+1$) $^+$.

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-hydroxy-piperidin-1-yl)-methanone (Compound No 23)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.33 (s, 1H), 6.86-7.13 (d, 2H), 4.8 (s, 1H), 4.37 (d, 1H) 3.87 (s, 3H), 3.1 (d, 1H), 1.85-2.01 (m, 8H) 1.25-1.56 (m, 12H). Mass spectroscopy showed the following peaks (m/z): 402.4 (M^+), 403.4 ($\text{M}+1$) $^+$.

WO 2005/021515

PCT/IB2004/002804

{4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-[1,4]diazepan-1-yl}-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 19)

Analysis by mass spectroscopy showed the following peaks (m/z): 702 (M^+), 703.4 (M+1)⁺.

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl-(2-methoxy methyl-pyrrolidin-1-yl)-methanone (Compound No. 37)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): δ 7.33 (s, 1H), 7.05-7.08 (d, 1H), 6.83-6.86 (d, 1H), 4.80 (s, 1H), 4.11-4.20 (d, 2H), 3.87 (s, 3H), 3.55-3.84 (m, 1H), 3.35-3.40 (d, 1H), 3.18 (s, 3H), 3.06-3.12 (d, 1H), 1.54-2.00 (m, 17H). Mass spectroscopy showed the following peaks (m/z): (416) (M^+), 417.50 (M+1)⁺.

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(3-hydroxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 31)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): δ 7.307 (d, 1H), 7.036-7.064 (d, 1H), 6.820-6.848 (d, 1H), 4.783 (s, 1H), 4.14-4.28 (m, 3H), 3.85 (s, 3H), 3.6-3.66 (m, 3H), 3.13-3.19 (m, 1H), 1.54-2.02 (m, 15H). Mass spectroscopy showed the following peaks (m/z): 402 (M^+), 403.400 (M+1)⁺.

Example 2: [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperazin-1-yl-methanone (Compound No.17)

Trifluoroacetic acid (0.13 mL, 1.6825 mmole) was added to a solution of Compound No.1 (0.1639 g, 0.3365 mmole) in dichloromethane (3 mL) and the reaction mixture was stirred at room temperature for 4.5 hour. The reaction was quenched by adding water (10 mL) and the reaction mixture was made basic by adding sodium bicarbonate solution. The resulting mixture was extracted with ethyl acetate (2×10 mL). Ethyl acetate layer was washed with water, dried over anhydrous sodium sulphate, filtered and finally concentrated under reduced pressure to afford a semi-solid residue, which on treatment with hexane, afforded the title organic compound.

WO 2005/021515

PCT/IB2004/002804

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.33 (d, 1H), 7.07-7.09 (d, 1H), 6.84-6.86 (d, 1H), 4.80 (s, 1H), 4.33-4.39 (d, 1H), 3.88 (s, 3H), 3.09-3.14 (d, 1H), 2.8-2.9 (m, 4H), 1.62-2.05 (m, 15H). Mass spectroscopy showed the following peaks (m/z): 387 (M) $^+$, 388.1 ($\text{M}+1$) $^+$.

5
Example 3: 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-cyclopropylmethyl-piperazin-1-yl)-methanone (Compound No. 20)

Anhydrous potassium carbonate (0.1368 g, 0.992 mmol) was added to a stirred solution of Compound No. 17 (0.048 g, 0.1240 mmol) and cyclopropyl methyl chloride (25 μL , 0.2728 mmol) in dry acetone (4 mL). The resulting mixture was refluxed in an oil bath and the temperature was maintained at 50-55 $^\circ\text{C}$ for 24 hour. The reaction was quenched by adding water (20 mL). The resulting mixture was extracted with ethyl acetate (2 \times 10 mL). The ethyl acetate layer was washed with water and dried over anhydrous potassium carbonate. The organic layer was concentrated under reduced pressure to afford the title organic
15 compound.

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.33(s, 1H), 7.07-7.09(d, 1H), 6.83-6.86(d, 1H), 3.8(s, 3H), 3.08-3.14(d, 1H), 1.33-1.85(m, 21H), 0.07-0.56(m, 5H).

20 Example 4: [1-4]-Bipiperidinyl-1-yl-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4-,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 14)

Thionyl Chloride (0.186 g, 1.57 mmoles, 10 eq) was added to a solution of compound of Formula VI (0.05 g) in acetonitrile (1.5 mL) and the solution refluxed at 70-72 $^\circ\text{C}$ for 3 hours. The solvent was removed under reduced pressure and excess of thionyl chloride was azeotropically distilled off using toluene. The resulting product was taken in dichloromethane (2 mL) and to this was added 4-piperidino-piperazine (0.0526 g) and triethyl amine (0.13 mL). The reaction mixture was stirred for 19 hours at room temperature. The resulting reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated. The
30 crude organic compound was obtained and purified by column chromatography using methanol:ethyl acetate [1:10] solvent system as eluent. Yield = 0.038 gm.

WO 2005/021515

PCT/IB2004/002804

Analysis by ^1H NMR spectroscopy showed the following peaks: 7.32-7.35 (d, 1H), 7.07-7.10 (d, 1H), 6.84-6.87 (d, 1H), 4.8 (s, 1H), 4.7 (m, 2H), 4.35-4.40 (m, 2H), 3.88 (s, 3H), 3.07-3.13 (m, 1H), 1.5-2.07 (m, 27H). Mass spectroscopy showed the following peaks (m/z): 469 (M) $^+$, 470.1 (M+1) $^+$.

5

Example 5: [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-pyrrolidin-1-yl-methanone (Compound No. 3)

The compound of Formula XIV (70 mg, 0.193 mmol, 1 eq.) was taken in dimethyl formamide (0.7 mL) followed by the addition of pyrrolidine (0.035 mL, 0.424 mmol, 2.2 eq). The reaction mixture was cooled to 0 °C and to this was added hydroxy benzotriazole (52 mg, 0.385 mmol, 2 eq) and N-methyl morpholine (0.84 mL, 0.77 mmol, 4 eq) and stirred for 1 hour at 0 °C. To this was added 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC·HCl) (81.33 mg, 0.424 mmol, 2.2 eq) at 0 °C with constant stirring. The reaction was allowed to warm to room temperature followed by stirring for 24 hours.

15 The reaction mixture was diluted with water (10 mL) and the organic compound was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude compound thus obtained was purified by column chromatography.

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.323-7.327 (d, 1H, Ar), 7.07-7.10 (dd, 1H), 6.83-6.86 (d, 1H, Ar), 4.79-4.81 (m, 1H), 3.84-3.98 (m, 5H, OCH_3 , CH_2), 3.43-3.55 (m, 8H), 2.9-3.04 (d, 1H), 2.84-2.89 (d, 1H), 1.77-1.97 (m, 16H). Mass spectroscopy showed the following peaks (m/z): 469(M) $^+$, 470.1 (M+1) $^+$.

20

Particular analogs of [3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-pyrrolidin-1-yl-methanone (Compound No.3), which are described below, can be prepared by reaction of a compound of Formula VI with corresponding cyclic amines.

25

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-piperidin-1-yl-methanone (Compound No. 4)

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): δ 7.325 (d, 1H), 7.09-7.11 (d, 1H, Ar), 6.83-6.85 (d, 1H, Ar), 4.79-4.816 (m, 1H), 3.96-4.05 (m, 2H), 3.87

30

WO 2005/021515

PCT/IB2004/002804

(s, 3H, -OCH₃), 3.44-3.60 (m, 8H), 2.99 (s, 2H), 1.49-2.01 (m, 20H). Mass spectroscopy showed the following peaks (m/z): 497 (M)⁺, 498.2 (M+1)⁺.

[3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(pyrrolidin-2-carboxylic acid methyl ester-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-[pyrrolidine-2-carboxylic acid methyl ester-5-yl]-ethanone (Compound No. 5)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): δ 7.26-7.32 (m, 1H), 7.02-7.11 (m, 1H), 6.8-6.86 (m, 1H), 4.79 (m, 1H), 4.56-4.58 (m, 2H), 3.8-8.6 (s, 3H, -OCH₃), 3.5-3.78 (m, 8H), 2.84-3.59 (m, 6H), 1.83-2.1 (m, 16H). Mass spectroscopy showed the following peaks (m/z): 585 (M)⁺, 586.2 (M+1)⁺.

[5-[4-(4-Chlorophenyl)-4-hydroxy-piperidine-1-carbonyl]-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazol-5-yl]-[4-(4-chlorophenyl)-4-hydroxy-piperidin-1-yl]-methanone (Compound No. 6)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): δ 7.27-7.44 (m, 11H, ArH), 7.08-7.11 (d, 1H, Ar), 6.84-6.87 (d, 1H, Ar), 4.73-4.81 (m, 1H), 4.51-4.54 (m, 2H), 4.08 (m, 5H, OCH₃, CH₂), 3.00-3.92 (m, 8H), 1.58-2.15 (m, 16H). Mass spectroscopy showed the following peaks (m/z): 749 (M)⁺, 750.1 (M+1)⁺.

1-{1-[5-(4-Acetyl-4-phenyl-piperidine-1-carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazole-5-carbonyl]-4-phenyl-piperidin-4-yl}-ethanone (Compound No. 2)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): δ 7.28-7.35 (m, 11H, ArH), 7.015-7.078 (d, 1H, ArH), 6.804-6.85 (d, 1H, ArH), 4.677-4.807 (m, 1H, CH), 4.184-4.22 (m, 2H), 3.861 (s, 1H, -OCH₃), 3.38-3.44 (m, 2H), 2.32-3.15 (m, 8H), 1.8-2.08 (m, 22H). Mass spectroscopy showed the following peaks (m/z): 733 (M)⁺, 734.4 (M+1)⁺.

WO 2005/021515

PCT/IB2004/002804

[3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(4-carboxylic acid tert butyl-ester-piperazin-1-yl-carbonyl)-4,5-dihydroisoxazol-5-yl]-{(4-carboxylic-acid-tert butyl ester piperazine-1-yl) ethanone (Compound No. 1)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): δ 7.26-7.31 (d, 1H, ArH), 7.06-7.09 (d, 1H, Ar), 6.87-6.84 (d, 1H, Ar), 4.81 (m, 1H, CH₂), 4.11-4.13 (m, 1H, CH₂), 3.88 (s, 3H, -OCH₃), 3.48-3.68 (m, 16H, 8 x NCH₂) 2.96-3.05(m, 2H, 2xCH₂), 1.85-1.97 (m, 8H, 4 x CH₂), 1.47 (s, 19H, 9xCH₃). Mass spectroscopy showed the following peaks (m/z): 699 (M)⁺, 700.600 (M+1)⁺.

[5-(5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-(carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-,5-dihydro-isoxazol-5-yl]-5-benzyl-2,5-diazabicyclo-[2.2.1]hept-2-yl-ethanone (Compound No 8)

Analysis by ¹H NMR spectroscopy showed the following peaks (DMSO): δ 6.99-7.34 (m, 13H, Ar), 4.809 (m, 1H), 4.4-4.53 (d, 1H), 3.5-3.91 (m, 13H), 2.7-3.08 (m, 5H), 1.56-1.8 (m, 16H). Mass spectroscopy showed the following peaks (m/z): 703 (M)⁺, 704.4 (M+1)⁺.

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(hydroxymethyl-piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-(4-hydroxymethyl-piperidin-1-yl)-ethanone (Compound No. 7)

Analysis by ¹H NMR spectroscopy showed the following peaks (CDCl₃): δ 7.26-7.34(m, 1H), 7.08-7.11(d, 1H), 6.83-6.85(d, 1H), 4.79(s, 1H), 3.87-3.96(m, 5H, 3xOCH₃, CH₂), 3.36-3.68(m, 8H), 2.8-3.05(m, 4H), 1.67-1.89(m, 20H).

EXAMPLE 6: 3-[3-Cyclopentyloxy-4-methoxy-phenyl]-7-methyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-6,9-dione (Compound No. 36)

To a solution of the compound of formula XIII (0.070g, 0.016 mmole, 1.0eq) in dimethylformamide (1.0mL), was added methyl amine (0.015g, 0.16mmol, 10.0eq) and stirred the reaction mixture at 100 °C overnight. The resulting reaction mixture was diluted with water (10.0 mL) and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound. Yield: 50%.

WO 2005/021515

PCT/IB2004/002804

M.P. 169-170°C.

Mass (m/z): 359.0 ($M^+ + 1$).

^1H NMR (CDCl_3): δ 7.3545 (d, 1H, Ar), 6.99-7.02 (d, 1H, Ar), 6.84-6.86 (d, 1H, Ar), 4.80-4.82 (m, 1H), 3.94-4.00 (d, 1H), 3.88 (s, 1H, OCH_3), 3.36-3.41 (m, 1H), 3.18-3.24 (m, 1H),
 3.09 (s, 3H, $-\text{NCH}_3$), 2.8-2.83 (m, 1H), 1.59-2.01 (m, 8H).

EXAMPLE 7: 3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-carbonyl]-bicyclo[2.2.1]heptan-2-one (Compound No. 34)

The title compound was prepared following the procedure as described for the synthesis of the compound of Formula V, by using 3-methylene-2-norbornenone in place of methyl methacrylate.

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): 7.34 (s, 1H), 7.0-7.03 (d, 1H), 6.82-6.85 (d, 1H), 4.80-4.81 (m, 1H), 3.82 (s, 3H), 3.24-3.43 (m, 2H), 2.68-2.75 (d, 2H), 2.40-2.43 (d, 1H), 1.43-2.01 (m, 12H). Mass spectroscopy showed the following peaks (m/z): 355 (M^+), 356.5 ($M+1$) $^+$.

EXAMPLE 8: 3-[3-Cyclopentyloxy-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4] non-2-ene-6-one (Compound No. 35)

The title compound was synthesized following the procedure as described for the synthesis of compound of Formula V, by using α -methylene- γ -butyrolactone in place of methyl methacrylate. The product had a melting point of 152.5-152.7°C.

Analysis by ^1H NMR spectroscopy showed the following peaks (CDCl_3): 7.36 (d, 1H), 7.05 (d, 1H), 6.84-6.87 (d, 1H), 4.81-4.82 (m, 1H), 4.44-4.54 (m, 2H), 3.86-3.91 (m, 4H), 3.32-3.38 (d, 1H), 2.69-2.71 (m, 1H), 2.37-2.41 (m, 1H), 1.78-1.79 (m, 8H). Mass spectroscopy showed the following peaks (m/z): 331 (M^+), 332.3 ($M+1$) $^+$.

EXAMPLE 9: 4-Difluoromethoxy-3-hydroxy-benzaldehyde and 3,4-bis-difluoromethoxy-benzaldehyde

To a solution of the compound 3,4-dihydroxy benzaldehyde (commercially available) (0.072 mole) in dimethylformamide (70 mL), benzyltriethyl ammonium chloride (0.036 mole) was added. To the resulting reaction mixture was added sodium hydroxide solution (0.0018 mole of 30% solution) dropwise for about 3 minutes with a continuous flow of chloro-

WO 2005/021515

PCT/IB2004/002804

difluoro methane. The reaction mixture was acidified with dilute hydrochloric acid and diluted with water. The reaction mixture was extracted with ethyl acetate, washed with saturated solution of sodium chloride and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compounds.

5

EXAMPLE 10: 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 38)

Step a: Synthesis of 3-cyclopentyloxy-4-methoxy-benzaldehyde

To a solution of 3-hydroxy-4-methoxy-benzaldehyde (commercially available) (1 eq)
10 was taken in dimethylformamide (10 mL), was added potassium iodide (0.1 eq) and potassium carbonate (2 eq). The reaction mixture was stirred at 70 °C and cyclopentyl bromide (2 eq) was added dropwise. The resulting reaction mixture was stirred at 70-80 °C for 16 hours. The reaction mixture was cooled and diluted with water, extracted with ethyl acetate and washed with saturated solution of sodium chloride. The organic solvent was
15 removed under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound.

Step b: Synthesis of 3-cyclopentyloxy-4-methoxy-benzaldehyde oxime.

To a solution of the compound obtained from step a above (1 eq) in ethanol was added hydroxylamine hydrochloride (2 eq) and sodium acetate (2 eq). The reaction mixture was
20 stirred at room temperature for 2-3 hours. The organic solvent was removed under reduced pressure. The residue thus obtained was diluted with water and extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound.

**Step c: Synthesis of 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methoxy
25 carbonylmethyl-4,5-dihydro-isoxazol-5-carboxylic acid methyl ester**

To a solution of the compound obtained from step b above (1 eq) in tetrahydrofuran, was added dimethylitaconate (2 eq). The reaction mixture was stirred at 60 °C for 0.5 hours followed by the addition of sodium hypochlorite solution. The resulting reaction mixture was stirred at 60-70 °C for 5-6 hours. Tetrahydrofuran was removed under reduced pressure. The
30 residue thus obtained was diluted with water, extracted with ethyl acetate, washed with

WO 2005/021515

PCT/IB2004/002804

saturated sodium chloride solution and water. The reaction mixture was dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound.

Step d: Synthesis of 5-carboxymethyl-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazol-5-carboxylic acid

5 To a solution of the compound obtained from step c in tetrahydrofuran (1.0 eq), was added and lithium hydroxide (5.0 eq) in water (as 5N solution). The mixture was stirred at room temperature over night. The solvent was removed under reduced pressure and the residue thus obtained was diluted with water and acidified with drops of concentrated hydrochloric acid. The organic compound was extracted with ethyl acetate, washed with
10 brine, dried over anhydrous sodium sulphate and finally concentrated under reduced pressure to afford title organic compound.

Step e: Synthesis of 2-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-hydroxymethyl-4,5-dihydro-isoxazol-5-yl]-ethanol

To a solution of sodium borohydride (3 eq) in tetrahydrofuran, was added a solution of
15 the compound obtained from step d above (1 eq) in tetrahydrofuran. To the resulting reaction mixture was added ethereal solution of trifluoroborane (3 eq) at 0 °C and stirred for 14-16 hours at ambient temperature. Sodium hydroxide (1N) solution was added at 0 °C and stirred for 1 hour. The reaction mixture was diluted with ethylacetate and water. The combined extract was washed with saturated solution of sodium chloride and concentrated under
20 reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound.

Step f: Synthesis of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxaza-2-aza-spiro[4.4]non-2-ene

To a solution of the compound obtained from step e above (1 eq) in tetrahydrofuran
25 triphenylphosphine (1.12 eq) and succinimide (1 eq), was added diisopropyldiazadicarboxylate (1.14 eq). The reaction mixture was stirred at room temperature for overnight. The organic solvent was removed under reduced pressure and the residue thus obtained was purified by column chromatography to furnish the title compound. Mass (m/z): 318 ($M^+ + 1$).

WO 2005/021515

PCT/IB2004/002804

Particular analogs of 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 38) which are described below can be prepared by reacting appropriate benzaldehyde group with alkyl halide, alkaryl halide or cycloalkyl halide.

- 5 **3-(3-Cyclopropylmethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene**
(Compound No. 39)

Mass (m/z): 304.11 ($M^+ + 1$)

3-(4-Difluoromethoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene

- 10 Mass (m/z): 328.15 ($M^+ + 1$)

3-(4-Difluoro-3-butoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 41)

Mass (m/z): 342.17 ($M^+ + 1$)

- 15 **3-(4-Difluoromethoxy-3-isobutoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene**
(Compound No. 42)

Mass (m/z): 328.15 ($M^+ + 1$)

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 43)

- 20 Mass (m/z): 340.17 ($M^+ + 1$)

3-(3-Benzoyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 44)

- 25 Mass (m/z): 376.14

3-(4-Difluoromethoxy-3-cyclopentyloxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 45)

Mass (m/z): 354.11

30

WO 2005/021515

PCT/IB2004/002804

3-(3,4-Bis-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 46)

Mass (m/z): 366.18 ($M^+ + 1$).

5 3-(3-Benzyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 72)

Example 11: 5-(1,7-dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 73)

10 To a solution of the compound No. 72 (100 mg, 0.29 mmol) in methanol (5 mL), was added palladium on carbon (40 mg, 10%). The reaction mixture was evacuated with hydrogen gas and the resulting reaction mixture was allowed to stir at room temperature for 1 hour. The reaction mixture was filtered through celite pad. The filtrate was concentrated under reduced pressure to furnish the title compound. Yield = 48 mg.

15 Mass (m/z): 250.19 ($M^+ + 1$).

EXAMPLE 12: 4-(1,7-dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 52)

20 Step a: Synthesis of 3-(4-benzyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4]non-2-ene.

The title compound was prepared following the procedure as described for the synthesis of compound No. 38 by using benzyl bromide in place of cyclopentyl bromide.

Step b: Synthesis of 4-(1,7-dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol

25 The title compound was prepared following the procedure as described for the synthesis of compound No. 73, by using compound No. 50 in place of compound No 72.

Mass (m/z): 250 ($M^+ + 1$).

EXAMPLE 13: 3-(3-Ethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 63)

30 To a solution of the compound No. 73 (1 eq) in dimethylformamide (10 mL), was added potassium iodide (0.1 eq) and potassium carbonate (2 eq). The reaction mixture was

WO 2005/021515

PCT/IB2004/002804

stirred at room temperature and ethyl bromide (2 eq) was added. The reaction mixture was stirred for overnight at room temperature. The reaction mixture was cooled and diluted with water, extracted with ethylacetate and washed with saturated solution of sodium chloride. The organic solvent was removed under reduced pressure. The residue thus obtained was

5 purified by column chromatography to furnish the title compound. Yield = 90%.
Mass (m/z): 278.18 ($M^+ + 1$).

Analogues of 3-(3-ethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 63) described below, can be prepared by using appropriate alkyl halide or

10 cycloalkyl halide in place of ethyl bromide, respectively as applicable in each case.

3-(3-Butoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 47)

Mass (m/z): 342 ($M^+ + 1$)

15

3-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 48)

Mass (m/z): 380 ($M^+ + 1$)

20 **3-(4-Difluoromethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 49)**

Mass (m/z): 300.06 ($M^+ + 1$).

3-(3-Cycloheptyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 51)

25

Mass (m/z): 382.28 ($M^+ + 1$).

3-[3-(Indan-2-yloxy)-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 53).

30 Mass (m/z): 366.37 ($M^+ + 1$).

WO 2005/021515

PCT/IB2004/002804

3-(3,4-Dimethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 62)

Mass (m/z): 264.8 ($M^+ + 1$).

3-(4-Methoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No.

5 **64)**

Mass (m/z): 292.14 ($M^+ + 1$).

3-(3-Isopropoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 65)

10 Mass (m/z): 292.14 ($M^+ + 1$).

3-(3-Butoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 66)

Mass (m/z): 306.18 ($M^+ + 1$).

15 **3-(3-Isobutoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 67)**

Mass (m/z): 306.18 ($M^+ + 1$).

3-[4-Methoxy-3-(3-methyl-butoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene

20 **(Compound No. 68)**

Mass (m/z): 320.18 ($M^+ + 1$).

3-(3-Cyclohexyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 69)

25 Mass (m/z): 332.17 ($M^+ + 1$)

3-[4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 71)

Mass (m/z): 363.14 ($M^+ + 1$)

30

WO 2005/021515

PCT/IB2004/002804

3-(3-Benzoyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 72)Mass (m/z): 340.14 (M^+1)**5 EXAMPLE 14: 3-(4-Ethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 54)**

The title compound was prepared following the procedure as described in Example 13, by using compound No. 52 in place of compound No. 73. Yield = 79%.

Mass (m/z): 278.24 (M^+1).

10

Analogues of 3-(4-ethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 54) described below, can be prepared by using appropriate alkyl halide or cycloalkyl halide in place of ethyl bromide, respectively, as applicable in each case.

15 3-(3-Methoxy-4-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 55)Mass (m/z): 292.28 (M^+1).**20 3-(4-Isopropoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound 56)**Mass (m/z): 292.28 (M^+1).**25 3-(4-Butoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 57)**Mass (m/z): 366.18 (M^+1).

25

3-(4-Cyclopentyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 58)Mass (m/z): 318.27 (M^+1).

WO 2005/021515

PCT/IB2004/002804

3-(4-Isobutoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 59)

Mass (m/z): 306.25 ($M^+ + 1$).

5 **3-(4-Cyclohexyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 60)**

Mass (m/z): 332.25 ($M^+ + 1$).

10 **3-(4-Cyclopropylmethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 61)**

Mass (m/z): 304.24 ($M^+ + 1$).

EXAMPLE 15: 4-(Methylene-cyclohexyl)-carbamic acid tert-butyl ester.

Step a: synthesis of (4-hydroxy-cyclohexyl)-carbamic acid tert-butyl ester

15 To a solution of the compound trans-amino cyclohexanol hydrochloride (4.0 g, 26.4 mmol) in dichloromethane (100 mL), was added triethylamine (7.35 mL, 52.8 mmol) and stirred the reaction mixture for 30 min. The reaction mixture was cooled to 0 °C followed by the addition of tert-butyl dicarbonate (8.64 g, 39.6 mmol) in dichloromethane (10.0 mL). The resulting reaction mixture was stirred for 8 hours. The reaction mixture was diluted with
20 water and stirred vigorously for 30 minutes. The organic layer was separated, washed with water and brine and dried over anhydrous sodium sulphate. The organic layer was concentrated and purified by column chromatography to furnish the title compound.

Yield = 5.05 g

Step b: Synthesis of (4-oxo-cyclohexyl)-carbamic acid tert-butyl ester

25 To a solution of the compound obtained from step a above (5 g, 23.4 mmol) in dichloromethane (100 mL), was added pyridinium chlorochromate (7.6 g, 35.0 mmol) and celite (5.0g). The reaction mixture was stirred at room temperature for 2 hours. Dichloromethane was evaporated under reduced pressure and the residue was diluted with ethylacetate. The reaction mixture filtered through celite pad and concentrated under reduced
30 pressure. The crude compound thus obtained was purified by column chromatography to furnish the title compound.

WO 2005/021515

PCT/IB2004/002804

Yield: 3.5 g

Step c: Synthesis of 4-methylene-cyclohexyl-carbamic acid tert-butyl ester

Triphenylmethylphosphonium iodide (17.2 g, 42.5 mmol) and potassium tert-butoxide (4.13 g, 36.8 mmol) were taken together under nitrogen atmosphere and dry tetrahydrofuran (150 mL) was added at room temperature. The reaction mixture was stirred for 3 hours at room temperature. To the resulting reaction mixture was added a solution of the compound obtained from step b above in dry tetrahydrofuran under nitrogen atmosphere and cooled to 0 °C followed by stirring for 10 hours at room temperature. The reaction mixture was quenched with water (5.0 mL) and concentrated under reduced pressure. The residue thus obtained was dissolved in dichloromethane, washed with water, brine and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure and the residue thus obtained was purified by column chromatography to furnish the title compound. Yield = 2.1 g
Mass (m/z): 211 ($M^+ + 1$).

EXAMPLE 16: 2-(4-Methylene-cyclohexyl)-isoindole-1,3-dione

Aminocyclohexanol hydrochloride (6.3 g, 41.6 mmol) and triethylamine (11.6 mL, 83.1 mmol) were stirred in toluene (150 mL) at room temperature for 1 hour. To this was added phthalic anhydride (7.4 g, 49.9 mmol) and the reaction mixture was stirred at 120-130 °C. The by-product water was removed from the reaction mixture. Toluene was concentrated under reduced pressure. The crude compound thus obtained was purified by column chromatography using ether in hexane solvent mixture (2:1) as eluent to furnish the title compound (8.5 g, 84%).
Mass (m/z): 241 ($M^+ + 1$)

Example 17: [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-carbamic acid isopropyl ester (Compound No. 79)

To a solution of 4-methylene-cyclohexyl-carbamic acid tert-butyl ester (0.55 g, 2.62 mmol), 3-cyclopentyloxy-4-methoxy-benzaldehyde oxime (0.62 g, 2.62 mmol) and pyridine (1 mL) in 20% chloroform in dichloromethane (50 mL) at room temperature under nitrogen atmosphere was added sodium hypochlorite (4.1, 5.0 mL, 2.62 mmol) dropwise. The resulting reaction mixture was stirred for 15 hours at room temperature followed by the

WO 2005/021515

PCT/IB2004/002804

addition of sodium hypochlorite (4%, 5.0 mL, 2.62 mmol) dropwise. The resulting reaction mixture was stirred for 15 hours at room temperature followed by the addition of sodium hypochlorite (4%, 5 mL, 2.62 mmol). The reaction mixture was again stirred for 15 hours. The organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound. Yield = 0.85 g.

Mass (m/z): 445

Analogues of [3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-carbamic acid isopropyl ester (Compound No. 79) described below can be prepared by using appropriate methylene-cycloalkyl group in place of 4-methylene-cyclohexyl-8-carbonic acid tert-butyl ester, respectively, as applicable in each case.

7-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-oxa-6-aza-spiro[3.4]oct-6-ene (Compound No. 82)

Mass (m/z): 302 ($M^+ + 1$).

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-aza-spiro[4.5]dec-2-ene (Compound No. 83)

Mass (m/z): 332.22 ($M^+ + 1$).

EXAMPLE 18: 2-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-ene-8-yl]-isoindole-1,3-dione (Compound No. 81)

The title compound was prepared following the procedure as described in Example 15, by using 2-(4-methylene-cyclohexyl)-isoindole-1,3-dione in place of 4-methylene-cyclohexyl-carbamic acid tert-butyl ester. Yield; 0.9 g

Mass (m/z): 475 ($M^+ + 1$).

EXAMPLE 19: 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-ylamine (Compound No. 80)

To a solution of the compound No. 79 (0.26 g, 0.54 mmol) in dichloromethane (50 mL), was added methanolic hydrochloric acid (5.9 mL, 29.3 mmol) at 0 °C and the reaction

WO 2005/021515

PCT/IB2004/002804

mixture was stirred at room temperature for 7 hours. The resulting reaction mixture was concentrated under reduced pressure, washed with saturated sodium bicarbonate solution and extracted with ether. Organic layer was concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound. Yield:

5 0.19 g

Mass (m/z): 345 ($M^+ + 1$).

EXAMPLE 20: 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-7-carboxylic acid tert-butyl ester (Compound No. 84)

10 **Step a: Synthesis of 3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester**

To a solution of tert-butyl dicarbonate (9.06 g, 0.02325 mol) in dichloromethane (25 mL) at 0°C, was added a solution of R(+)-3-hydroxy pyrrolidine in dichloromethane (15 mL). The reaction mixture was stirred for 2 hours at ambient temperature. Reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with
15 water, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate in hexane (40:60) solvent mixture as eluent to furnish the title compound. Yield = 4.0 g

Step b: Synthesis of 3-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of the compound obtained from step a above (500 mg, 0.0027 mole) in
20 dichloromethane (10 mL) was added celite (400 mg) and stirred at room temperature for 10 minutes. Pyridinium chlorochromate (869 mg, 0.0040 mole) was added portionwise over a period of 5 minutes. The reaction mixture was stirred at room temperature for 3 hours. Dichloromethane was removed under reduced pressure followed by the addition of ethyl acetate. The resulting reaction mixture was again stirred for 10 minutes and filtered through
25 celite pad. The organic layer was removed under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate in hexane (30:70) solvent mixture as eluent to furnish the title compound. Yield: 350 mg

Step c: Synthesis of 3-methylene-pyrrolidine-1-carboxylic acid tert-butyl ester

The solution of a compound triphenylmethylphosphonium iodide (2.24 g, 0.0055
30 mole), potassium tert-butoxide (517 mg, 0.0046 mole) in tetrahydrofuran (10 mL) was stirred at -78°C for 20 minutes and then at room temperature for 1 hour. To the resulting reaction

WO 2005/021515

PCT/IB2004/002804

mixture was added a solution of 3-methylene-pyrrolidine-1-carboxylic acid tert-butyl ester (340 mg, 0.0018 mol) in tetrahydrofuran (10 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 10 min. followed by diluting it with water. Tetrahydrofuran was evaporated under reduced pressure, extracted with ethyl acetate, washed with anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using ethylacetate in hexane (10:90) solvent mixture as eluent. Yield: 170 mg.

Step d: Synthesis of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-7-carboxylic acid tert-butyl ester

The compound obtained from step c above (170 mg, 0.0010 mole) and 3-cyclopentyloxy-4-methoxy-benzaldehyde oxime (236 mg, 0.0010 mole) were taken in dichloromethane (20%) in chloroform followed by the addition of pyridine (2 drops). The reaction mixture was stirred at room temperature for 10 minutes followed by the addition of sodium hypochlorite (2 mL) dropwise. The resulting reaction mixture was stirred at room temperature for 4 hours. Tetrahydrofuran was evaporated under reduced pressure followed by diluting it with water. The compound was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound. Yield: 200 mg.

The analogues of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-7-carboxylic acid tert-butyl ester (Compound No. 84) described below, can be prepared by using appropriate piperidinyl group in place of 3-methylene-pyrrolidine-1-carboxylic acid tert-butyl ester.

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid tert-butyl ester (Compound No. 74)

EXAMPLE 21: 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene (Compound No. 85)

The title compound was prepared following the procedure as described in Example 19. Yield: 60%.

WO 2005/021515

PCT/IB2004/002804

Mass (m/z): 317.16 (M^+ -HCl).

The analogues of (Compound No. 85) described below, can be prepared by deprotecting appropriate amino group, respectively, as applicable in each case.

5 **Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene (Compound No. 75)**

Mass (m/z): 331.25 (M^+ -HCl).

10 **EXAMPLE 22: 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid-(2,6-difluoro-phenyl)-amide (Compound No. 77)**

To a solution of the compound No. 75 in dichloromethane (5 mL) was added 1,3-difluoro-2-isocyanato-benzene (0.2954 mol) and stirred the reaction mixture at room temperature for overnight. The reaction mixture was concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title
15 compound. Yield: 96 mg.

Mass (m/z): 486.07 (M^+ +1).

Analogues of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid-(2,6-difluoro-phenyl)-amide (Compound No. 77) described below, can be prepared by using appropriate isocyanate group in place of 1,3-difluoro-isocyanate-
20 benzene, respectively, as applicable in each case.

4-Chloro-N-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carbonyl]-benzene sulfonamide (Compound No. 76)

Mass (m/z): 548.01 (M^+ +1).

25

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid (2,6-difluoro-phenyl)-amide (Compound No. 77)

Mass (m/z): 486.07 (M^+ +1).

WO 2005/021515

PCT/IB2004/002804

EXAMPLE 23: Efficacy of Compounds as PDE IV InhibitorsPDE-IV Enzyme Assay

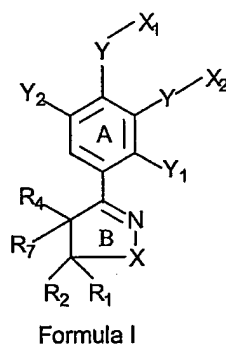
- The efficacy of compounds as PDE-4 inhibitor was determined by an enzyme assay (Burnouf *et al.*; *J. Med. Chem.*, 2000, 43:4850-4867). The PDE-4 enzyme source used was
- 5 U937 cell cytosolic fraction prepared by sonication. The enzyme reaction was carried out, with the cytosolic fraction as the enzyme source, in the presence of cAMP (1 μ M) at 30 °C in the presence or absence of NCE for 45 -60 min. An aliquot of this reaction mixture was taken further for the ELISA assay to determine level of cAMP in the sample. The concentration of the cAMP in the sample directly correlates with the degree of PDE-4 enzyme inhibition.
- 10 Results were expressed as percent control and the IC₅₀ values of test compounds were reported to be in the range of μ M to low nM.

WO 2005/021515

PCT/IB2004/002804

We Claim:

1. A compound having the structure of Formula I,



and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides, wherein

X is oxygen;

R₁ is hydrogen; alkyl; heterocyclyl; $(CH_2)_{1-4} OR'$, provided that **R₂** also is $(CH_2)_{1-4} OR'$; $-C(=O)NR_xR_y$, provided that **R₂** also is $-C(=O)NR_xR_y$; or $-(CH_2)_m-C(=O)R_3$;

R₂ is $-(CH_2)_m-C(=O)R_3$; $-(CH_2)_{1-4} OR'$, provided **R₁** also is $(CH_2)_{1-4} OR'$; $-C(=O)NR_xR_y$ provided **R₁** also is $-C(=O)NR_xR_y$, or **R₁** and **R₂** together forms an optionally substituted cycloalkyl or heterocyclyl ring wherein the optional substituent is oxo, alkyl, alkenyl, alkynyl, halogen, nitro, $-NH_2$, $-C(=O)NR_xR_y$, $-NHCOOR_6$, cyano, hydroxy, alkoxy, or substituted amino;

R₄ is hydrogen; alkyl; $-OR_5$; halogen; $-NH_2$, substituted amino; cyano; carboxy; or $-C(=O)NR_xR_y$; or **R₂** and **R₄** forms an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s) selected from the group consisting of N, O and S, wherein the substituents is one or more of alkyl, halogen, hydroxy, alkoxy, $-NH_2$ or substituted amino, with the proviso that **R₂** and **R₄** together does not form $-CH_2-O-CH_2-O-CH_2-$;

WO 2005/021515

PCT/IB2004/002804

R_7 is hydrogen, alkyl, alkenyl, alkynyl, $-OR_5$, halogen, cyano, $-NH_2$ or substituted amino;

X_1 and X_2 are each independently hydrogen, alkyl, alkaryl, cycloalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl;

Y is an oxygen atom; a sulphur atom; or $-NR$;

Y_1 and Y_2 are each independently hydrogen; alkyl; $-OR$; $-SR$; or $-NHR$;

wherein any of Y_1 and X_2 & X_1 and Y_2 together optionally form a cyclic ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms such as N, O and S;

X_1 and X_2 together optionally forms a cyclic ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms such as N, O and S,

wherein the halogen is F, Cl, Br, or I; R' is alkyl, alkenyl, alkynyl, saturated or unsaturated cycloalkyl, aryl, heterocyclyl or heteroaryl; R_x and R_y are each independently hydrogen, alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, cycloalkyl, $-SO_2R_5$, aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl; m is an integer between 0-2; R_3 is optionally substituted R_p or R_q ; R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclylalkyl; and R is hydrogen, acyl, aryl, or alkyl; and

wherein R_5 is hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl; R_p is heterocyclyl or heteroaryl ring, wherein the rings are attached to $(CH_2)_mC(=O)$ through N, and R_q is heterocyclyl or heteroaryl ring wherein the said rings are attached to $-(CH_2)_mC(=O)$ through C.

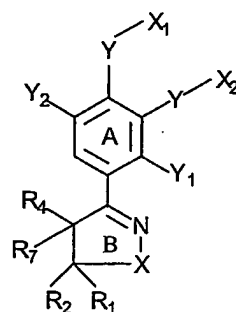
WO 2005/021515

PCT/IB2004/002804

3. The compound according to claim 1, wherein Y is oxygen or -NR.
4. The compound according to claim 1, wherein Y₁ and Y₂ are each independently hydrogen, alkyl or -OR.
5. The compound according to claim 1, wherein X₁ and X₂ are each independently methyl, ethyl, butyl, propyl, isopropyl, isobutyl, morpholinylmethyl, difluoromethyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, cycloheptyl, indanyl, adamantyl and benzyl.
6. The compound according to claim 1, wherein X and Y are independently oxygen, X₁ and X₂ are independently optionally substituted alkyl, cycloalkyl, heterocyclalkyl or alkaryl; R₁ and R₂ are independently alkyl or -(CH₂)_mC(=O)R₃, wherein R₃ is R_p, or R₁ and R₂ together join to form optionally substituted cycloalkyl and heterocycl ring; and Y₁, Y₂, R₄ and R₇ are each hydrogen.
7. The compound according to claim 5, wherein R_p is an optionally substituted heterocycl ring selected from piperazinyl, piperidinyl, pyrrolidinyl, homopiperazinyl, or diaza-bicycloheptane.
8. The compound according to claim 1, wherein X₁ and X₂ together form a cycloalkyl ring selected from the group consisting of cyclohexyl, cyclobutyl and cyclopentyl; or a heterocycl ring selected from the group consisting of tetrahydrofuran, piperidine, pyrrolidine and tetrahydropyranyl.
9. The compound according to claim 1, wherein optional substituents on R₁ and R₂ are -NH₂, difluorophenylaminocarbonyl, dichlorophenylaminocarbonyl, indanedione, tertbutylcarbamate, carboxy, tert-butoxycarbonyl or chlorophenylsulphonamidocarbonyl.
10. The compound according to claim 1, wherein X₁ and X₂ may together form a cyclic ring fused with the ring A containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms such as N, O and S.
11. A compound having the structure of Formula I,

WO 2005/021515

PCT/IB2004/002804



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides, wherein

X is NR₇ or S;

R₇ is hydrogen or (C₁-C₆)-alkyl;

R₁ and R₂ are each independently alkyl; alkenyl; alkynyl; alkoxy; hydroxy; cyano; nitro; halogen; heteroaryl; heterocyclyl; heteroarylalkyl; heterocyclalkyl; -NH₂; substituted amino; carboxy; -(CH₂)_m(C=O)R₃; -C(=O)NR_xR_y; or -(CH₂)₁₋₄OR', or R₁ and R₂ may together form optionally substituted cycloalkyl or heterocyclyl ring wherein the substituents of such a joint R₁-R₂ ring(s) can be oxo, alkyl, alkenyl, alkynyl, halogen, nitro, -NH₂, -C(=O)NR_xR_y, -NHCOOR₆, cyano, hydroxy, alkoxy, or substituted amino;

R₄ is hydrogen; alkyl; halogen; -OR₅; cyano; carboxy; -NH₂, substituted amino, or -C(=O)NR_xR_y, or R₂ and R₄ may together form an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatoms, wherein the heteroatom is N, O or S, with the proviso that R₂ and R₄ together does not form -CH₂-O-CH₂-O-CH₂-, and wherein the substituents is one or more of alkyl, halogen, hydroxy, alkoxy, or amino;

R₇ is hydrogen, alkyl, alkenyl, alkynyl, -OR₅, halogen, cyano, -NH₂ or substituted amino;

WO 2005/021515

PCT/IB2004/002804

X_1 and X_2 are each independently alkyl, cycloalkyl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclalkyl;

Y is an oxygen atom; a sulphur atom; or $-NR$;

Y_1 and Y_2 are each independently hydrogen; alkyl; $-OR$; $-SR$; or $-NHR$;

any of Y_1 and X_2 & X_1 and Y_2 optionally together form a cyclic ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms selected from the group consisting of N, O and S; and

X_1 and X_2 optionally together form a cyclic ring fused with the ring A shown in Formula I, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms selected from the group consisting of N, O and S;

wherein the halogen is F, Cl, Br, or I; R_3 is optionally substituted R_p or R_q ; R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclalkyl; R is hydrogen, acyl, aryl or alkyl; m is an integer between 0-2; R_3 is optionally substituted R_p or R_q ; R' is alkyl, alkenyl, alkynyl, saturated or unsaturated cycloalkyl, aryl, heterocyclyl or heteroaryl; and R_x and R_y are each independently hydrogen, alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, cycloalkyl, $-SO_2R_5$, aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclalkyl;

wherein R_5 is hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl; R_p is heterocyclyl or heteroaryl ring, wherein the rings are attached to $(CH_2)_mC(=O)$ through N, and R_q is heterocyclyl or heteroaryl ring wherein the said rings are attached to $-(CH_2)_mC(=O)$ through C.

12. A compound which is selected from:

[3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(4-carboxylic acid tert butyl-ester-piperazin-1-yl-carbonyl)-4,5-dihydroisoxazol-5-yl]-(4-carboxylic-acid-tert butyl ester piperazine-1-yl) ethanone (Compound No. 1),

1-{1-[5-(4-Acetyl-4-phenyl-piperidine-1-carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazole-5-yl]-4-acetyl-4-phenyl-piperidin-4-yl]-ethanone (Compound No. 2),

WO 2005/021515

PCT/IB2004/002804

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-pyrrolidin-1-yl-ethanone (Compound No. 3)

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-piperidin-1-yl-ethanone (Compound No. 4),

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(pyrrolidin-2-carboxylic acid methyl ester-1-carbonyl)-4,5-dihydro-isoxazol-5-yl)-[pyrrolidine-2-carboxylic acid methyl ester-5-yl] ethanone (Compound No 5),

[5-[4-(4-Chlorophenyl)-4-hydroxy-piperidine-1-carbonyl]-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazol-5-yl]-[4-(4-chlorophenyl)-4-hydroxy-piperidin-1-yl]-ethanone (Compound No.6),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(hydroxymethyl-piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-(4-hydroxymethyl-piperidin-1-yl)-ethanone (Compound No. 7),

[5-(5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-(carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-,5-dihydro-isoxazol-5-yl]-5-benzyl-2,5-diazabicyclo-[2.2.1]hept-2-yl-ethanone (Compound No 8),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperidin-1-yl-methanone (Compound No. 9),

4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester (Compound No. 10),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-carbonyl]-pyrrolidin-2-carboxylic acid (Compound No. 11),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester (Compound No. 12),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-yl]-pyrrolidin-1-yl-methanone (Compound No. 13),

[1-4]-Bipiperidiny-1-yl-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 14),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-4-phenyl-piperidine-4-yl}-ethanone (Compound No.15),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-methyl-piperazin-1-yl)-methanone (Compound No. 16),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperazin-1-yl-methanone (Compound No.17),

WO 2005/021515

PCT/IB2004/002804

[4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-methanone (Compound no. 18),

{4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-[1,4]diazepan-1-yl}-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 19),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-cyclopropylmethyl-piperazin-1-yl)-methanone (Compound No. 20)

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-isobutyl-1-piperazin-1-yl)-methanone (Compound No.21),

[3-Hydroxymethyl-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 22),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-hydroxy-piperidin-1-yl)-methanone (Compound No 23),

(4-Benzyl-piperidin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No 24),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperidin-4-one (Compound No. 25),

[4-(4-Bromophenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No 26),

(5-Benzyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 27)

(4-Benzyl-piperazin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 28),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-pyrrolidin-2-carboxylic acid methyl amide (Compound No. 29),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-pyrrolidine-2-carboxylic acid diethyl amide (Compound No. 30),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(2-hydroxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 31),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonyl]-piperidine-2-carboxylic acid methyl ester (Compound No. 32)

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carboxyl]-pyrrolidine-2-carboxylic acid amide (Compound No. 33),

WO 2005/021515

PCT/IB2004/002804

3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-bicyclo[2.2.1]heptan-2-one (Compound No. 34),

3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-en-6-one (Compound No. 35),

3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-7-methyl-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-6,9-dione (Compound No. 36),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl-(2-methoxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 37)

3-(3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 38),

3-(3-(3-Cyclopropylmethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 39),

3-(4-Difluoromethoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 40),

3-(4-Difluoro-3-butoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 41),

3-(4-Difluoromethoxy-3-isobutoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 42),

3-(3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 43),

3-(3-(3-Benzyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 44),

3-(4-Difluoromethoxy-3-cyclopentyloxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 45),

3-(3,4-Bis-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 46),

3-(3-(3-Butoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 47),

3-[3-(Bicyclo[2.2.1]hept-2-yl-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 48),

3-(4-Difluoromethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 49),

WO 2005/021515

PCT/IB2004/002804

3-(4-Benzoyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 50),

3-(3-Cycloheptyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 51),

4-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 52),

3-[3-(indan-2-yloxy)-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 53)

3-(4-Ethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 54),

3-(3-Methoxy-4-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 55),

3-(4-Isopropoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 56),

3-(4-Butoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 57),

3-(4-Cyclopentyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 58),

3-(4-(Isobutoxy)-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 59),

3-(4-Cyclohexyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 60),

3-(4-Cyclopropylmethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 61),

3-(3,4-Dimethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 62),

3-(3-Ethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 63),

3-(4-Methoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 64),

3-(3-Isopropoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 65),

3-(3-Butoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 66),

WO 2005/021515

PCT/IB2004/002804

3-(3-Isobutoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 67),

3-[4-Methoxy-3-(3-methyl-butoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 68),

3-(3-Cyclohexyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 69),

3-(3-Cycloheptyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 70),

3-[4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 71),

3-(3-Benzoyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 72),

5-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 73),

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid isopropyl ester (Compound No. 74),

Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene (Compound No. 75),

4-Chloro-N-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carbonyl]-benzene sulfonamide (Compound No. 76),

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid-(2,6-difluoro-phenyl)-amide (Compound No. 77),

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid-(2,4-dichloro-phenyl)-amide (Compound No. 78),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-carbamic acid isopropyl ester (Compound No. 79),

Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-ylamine (Compound No. 80),

2-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-isoindole-1,3-dione (Compound No. 81),

7-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-oxa-6-aza-spiro[3.4]oct-6-ene
(Compound No. 82),

WO 2005/021515

PCT/IB2004/002804

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-ene
(Compound No. 83),

3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-7-
carboxylic acid tert-butyl ester (Compound No. 84),

Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-
spiro[4.4]non-2-ene (Compound No. 85).

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, 10 or 11 together with a pharmaceutically acceptable carrier, excipient or diluent.

14. A method of treating AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis or other inflammatory diseases in an animal or human comprising administering to said animal or human a therapeutically effective amount of a compound of claim 1, 10 or 11.

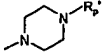
15. A method of preventing, inhibiting or suppressing inflammatory condition in an animal or human comprising administering to said animal or human a therapeutically effective amount of a compound of claim 1, 10 or 11.

16. A method for preparing a compound of Formula XI, its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides wherein the method comprises the steps of:

- g. reacting a compound of Formula II with hydroxylamine hydrochloride in the presence of an acetate to form a compound of Formula III;
- h. reacting the compound of Formula III with a compound of Formula IV to form a compound of Formula V;
- i. hydrolyzing the compound of Formula V to form a compound of Formula VI;

WO 2005/021515

PCT/IB2004/002804

- j. reacting the compound of Formula VI with a compound of Formula VII, wherein R_p is , to form a compound of Formula IX; or reacting the compound of Formula VI with thionyl chloride to give a compound of Formula VIII, which is reacted with a compound of Formula VII to form a compound of Formula IX;
- k. deprotecting the compound of Formula IX to form Formula X; and
- l. reacting the compound of Formula X with Hal- R_p' , wherein R_p' is alkyl or acyl and Hal is halogen, to form a compound of Formula XI.
17. The method of claim 15, wherein the acetate is sodium acetate.
18. The method of claim 15, wherein the compound of Formula V is hydrolyzed in the presence of basic hydrolyzing agent.
19. The method of claim 17, wherein the basic hydrolyzing agent is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide and a mixture thereof.
20. The method of claim 15, wherein the compound of Formula VI is reacted with the compound of Formula VII in the presence of a condensing agent and in the presence of a base.
21. The method of claim 19, wherein the condensing agent is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide, dicyclohexyl carbodiimide and a mixture thereof, and the base is selected from the group consisting of 1,8-diazabicyclo[5.4.0]undec-7-ene, N-methylmorpholine, triethylamine, diisopropylamine, pyridine, and a mixture thereof.
22. The method of claim 15, wherein the compound of Formula IX is deprotected in the presence of a deprotecting agent.
23. The method of claim 21, wherein the deprotecting agent is trifluoro acetic acid.

WO 2005/021515

PCT/IB2004/002804

24. The method of claim 15, wherein the compound of Formula VIII is reacted with a compound of Formula VII in the presence of a base.

25. The method of claim 23, wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, pyridine, and a mixture thereof.

26. A method for preparing a compound of Formula XV or Formula XVI and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:

- d. reacting a compound of Formula III with a compound of Formula XII to form a compound of Formula XIII;
- e. hydrolyzing the compound of Formula XIII to form a compound of Formula XIV; and
- f. reacting the compound of Formula XIV with a compound of Formula VII to form a compound of Formula XVI, or

reacting the compound of Formula XIV with methylamine to form a compound of Formula XVI.

27. The method of claim 25, wherein the hydrolysis of the compound of Formula XIII is carried out in the presence of a basic hydrolyzing agent.

28. The method of claim 26, wherein the basic hydrolyzing agent is selected from the group consisting of sodium hydroxide, lithium hydroxide, potassium hydroxide, and a mixture thereof.

29. The method of claim 25, wherein the reacting of the compound of Formula XIV with the compound of Formula VII is carried out in the presence of an organic base and a condensing agent.

30. The method of claim 28, wherein the organic base is selected from the group consisting of 1,8-diazabicyclo[5.4.0]undec-7-ene, N-methylmorpholine, diisopropylamine, pyridine, and a mixture thereof, and the condensing agent is selected

WO 2005/021515

PCT/IB2004/002804

from the group consisting of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride, dicyclohexylcarbodiimide, and a mixture thereof.

31. A method for preparing a compound of Formula XVIII and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of reacting a compound of Formula III with a compound of Formula XVII to form a compound of Formula XVIII.

32. A method for preparing a compound of Formula XXI and a compound of Formula XXII and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of reacting a compound of Formula XIX with a compound of Formula XX, wherein R_z is alkyl optionally substituted with halogen, to form a compound of Formula XXI and a compound of Formula XXII.

33. The method of claim 31, wherein the reaction of a compound of Formula XIX with a compound of Formula XX is carried out in the presence of a phase transfer catalyst

34. The method of claim 32, wherein the phase transfer catalyst is benzyl triethyl ammonium chloride.

35. A method of preparing a compound of Formula XXXI and a compound of XXXII and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:

- a. reacting a compound of Formula XXII, wherein R_z is alkyl optionally substituted with halogen, with a compound of Formula of XXIII, wherein R_{z1} is alkyl, alkaryl, or cycloalkyl, to form a compound of Formula XXIV;
- b. reacting the compound of Formula XXIV with hydroxylamine hydrochloride to form a compound of Formula XXV;
- c. reacting the compound of Formula XXV with a compound of Formula XXVI, wherein P is alkyl or alkaryl, to form a compound of Formula XXVII;

WO 2005/021515

PCT/IB2004/002804

- d. hydrolyzing the compound of Formula XXVII to form a compound of Formula XXVIII;
- e. reducing the compound of Formula XXVIII to form a compound of Formula XXIX;
- f. cyclization of the compound of Formula XXIX to form a compound of Formula XXX; and
- g. debenzylation of the compound of Formula XXX to form the compound of Formula XXXI, wherein R_z is benzyl and R_{z1} is alkyl optionally substituted with halogen, or debenzylation of the compound of Formula XXX to form the compound of Formula XXXII, wherein R_z is benzyl and R_{z1} is alkyl or cycloalkyl.

36. The method of claim 34, wherein the reaction of a compound of Formula XXII with a compound of Formula XXIII is carried out in the presence of a base.

37. The method of claim 34, wherein the base is selected from the group consisting of potassium carbonate, sodium carbonate, sodium bicarbonate, and a mixture thereof.

38. The method of claim 34 the compound of Formula XXVII is hydrolysed in the presence of a base.

39. The method of claim 37, wherein the base is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, and a mixture thereof.

40. The method of claim 34, wherein the compound of Formula XXVIII is reduced in the presence of a reducing agent.

41. The method of claim 39, wherein the reducing agent is sodium borohydride, sodium cyanoborohydride, and a mixture thereof.

42. The method of claim 34, wherein the compound of Formula XXIX undergoes cyclisation in the presence of a catalyst.

WO 2005/021515

PCT/IB2004/002804

43. The method of claim 41, wherein the catalyst is selected from the group consisting of triphenylphosphine, tri-tertbutyl phosphine, tri-cyclohexyl phosphine, and a mixture thereof.

44. The method of claim 34, wherein the compound of Formula XXX is debenzylated to form the compound of Formula XXXI, wherein R_{Z1} is benzyl and R_z is alkyl optionally substituted with halogen, or Formula XXXII, wherein R_{Z1} is benzyl and R_z is alkyl or cycloalkyl, in the presence of a deprotecting agent.

45. The method of claim 43, wherein the deprotecting agent is palladium on carbon.

46. A method of preparing a compound of Formula XXXIIa and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of debenylation of a compound of Formula XXXII to form a compound of Formula XXXIIa, wherein Z_3 is benzyl and R_z is alkyl or cycloalkyl.

47. The method according to claim 45, wherein the debenylation of the compound of Formula XXXII is carried out in the presence of a deprotecting agent or under hydrogenation transfer conditions.

48. The method of claim 46, wherein the deprotecting agent is hydrogen and palladium on carbon and the catalytic hydrogenation transfer conditions is a condition under ammonium formate and palladium on carbon.

49. A method of preparing a compound of Formula XXXIV and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of reacting a compound of Formula XXXI with a compound of Formula XXXIII to form a compound of Formula XXXIV.

50. The method of claim 48, wherein the reaction of a compound of Formula XXXI with a compound of Formula XXXIII is carried out in the presence of base.

WO 2005/021515

PCT/IB2004/002804

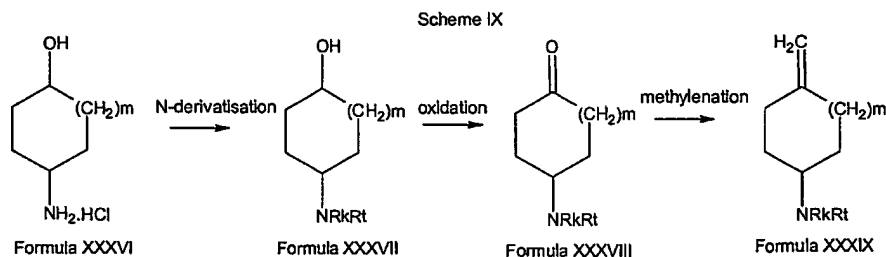
51. The method of claim 49, wherein the base is selected from the group consisting of potassium carbonate, sodium carbonate, sodium bicarbonate, and a mixture thereof.


52. A method of preparing a compound of Formula XXXV and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the step of reacting a compound of Formula XXXIIa with a compound of Formula XXXIII to form a compound of Formula XXXV.

53. The method of claim 51, wherein the reaction of a compound of Formula XXXIIa with a compound of Formula XXXIII is carried out in the presence of a base.

54. The method of claim 52, wherein the base is selected from the group consisting of potassium carbonate, sodium carbonate, sodium bicarbonate, and a mixture thereof.

55. A method of preparing a compound of formula XXXIX and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:



- a. N-derivatization of a compound of Formula XXXVI to form a compound of Formula XXXVII, wherein Rk is hydrogen and Rt is $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$ or Rk and Rt together joins to form  ;
- b. oxidation of the compound of Formula XXXVII to form a compound of Formula XXXVIII, wherein Rt is $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$; and
- c. methylenation of the compound of Formula XXXVIII to form a compound of Formula XXXIX.

WO 2005/021515

PCT/IB2004/002804

55. A method of claim 54, wherein the compound of Formula XXXVI is N-derivatised to form a compound of Formula XXXVII with tert-butyl dicarbonate and in the presence of a base.

56. The method of claim 55, wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, and a mixture thereof.

57. The method of claim 5, wherein the compound of Formula XXXVI is N-derivatised to form a compound of Formula XXXVII (wherein R_k) with phthalic anhydride in an organic solvent.

58. The method of claim 57, wherein the compound of Formula XXXVI is N-derivatised to give a compound of Formula XXXVII in the presence of a base selected from the group consisting of triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, and a mixture thereof.

59. The method of claim 54, wherein the oxidation of a compound of Formula XXXVII is carried out in the presence of an oxidizing agent.

60. The method of claim 59, wherein the oxidizing agent is selected from the group consisting of pyridinium chlorochromate, manganese dioxide, potassium permanganate, Jones reagent (CrO₃/H₂SO₄), and a mixture thereof.

61. The method of claim 54, wherein the methylenation of a compound of Formula XXXVIII is carried out in the presence of Wittig salt.

62. The method of claim 61, wherein the Wittig salt is selected from the group consisting of triphenylmethylphosphonium iodide, triphenylmethylphosphonium bromide, and a mixture thereof.

63. A method of preparing a compound of Formula XLII and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:

WO 2005/021515

PCT/IB2004/002804

a. reacting a compound of Formula XL with a compound of Formula XXV to form a compound of Formula XLI; and

b. deprotecting the compound of Formula XLI to form a compound of Formula XLII.

64. The method of claim 63, wherein the reaction of a compound of Formula XL with a compound of Formula XXV is carried out in the presence of a base.

65. The method of claim 64, wherein the base is selected from the group consisting of pyridine, N-methylmorpholine, triethylamine, diisopropylethylamine, and a mixture thereof.

66. A method of preparing a compound of Formula L and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides comprising the steps of:

a. N-protecting a compound of Formula XLIII to form a compound of Formula XLIV;

b. oxidizing the compound of Formula XLIV to form a compound of Formula XLV;

c. methylenation of the compound of Formula XLV to form a compound of Formula XLVI;

d. reacting the compound of Formula XLVI with a compound of Formula XXV to form a compound of Formula XLVII;

e. deprotecting the compound of Formula XLVII to form a compound of Formula XLVIII; and

f. reacting the compound of XLVIII with a compound of Formula XLIX to form a compound of Formula L.

67. The method of claim 66, wherein N-protection of a compound of Formula XLIII is carried out in the presence of a base.

WO 2005/021515

PCT/IB2004/002804

68. The method of claim 67, wherein the base is selected from the group consisting of triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, and a mixture thereof.

69. The method of claim 66, wherein the oxidation of a compound of Formula XLIV is carried out using an oxidizing agent.

70. The method of claim 69, wherein the oxidizing agent is selected from the group consisting of pyridinium chlorochromate, manganese dioxide, potassium permanganate, Jones reagent ($\text{CrO}_3/\text{H}_2\text{SO}_4$), and a mixture thereof.

71. The method of claim 66, wherein the methylenation of a compound of Formula XLV is carried out in the presence of a Wittig salt.

72. The method of claim 71, wherein the Wittig salt is selected from the group consisting of triphenylmethyl-phosphonium iodide, triphenylmethylphosphonium bromide, and a mixture thereof.

73. The method of claim 66, wherein the reaction of a compound of Formula XLVI with a compound of Formula XXV is carried out in the presence of a base.

74. The method of claim 73, wherein the base is selected from the group consisting of pyridine, N-methylmorpholine, diisopropylethylamine, triethylamine, and a mixture thereof.